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Effect of Triazolam on Pilot Performance

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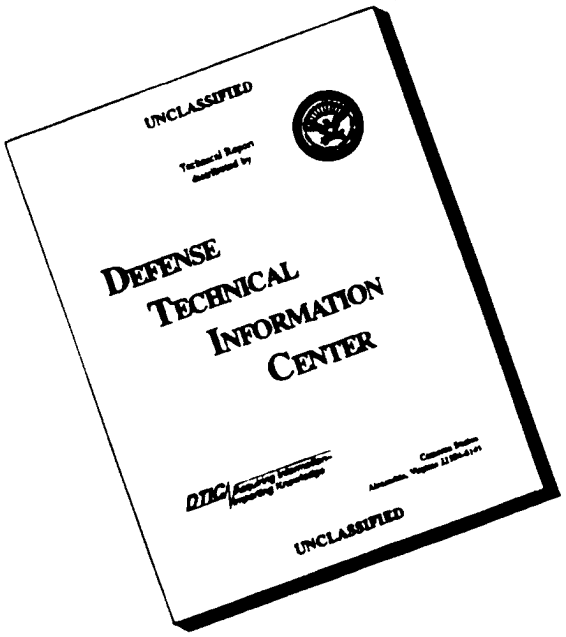

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This study was designed to determine if an aviator who has taken triazolam before bedtime could adequately perform his duties the following day after a full night of sleep. In addition, the project determined if an aviator who is awakened shortly after taking triazolam could perform his required tasks. It was hypothesized that a person who took triazolam in order to improve sleep quality may show more difficulty in performing a task immediately upon awakening than when awakened from sleep not induced with a hypnotic.

Ten U.S. Army aviators were tested over a 10-day period. After 3 days of training, each subject was administered triazolam (0.25 mg) on 2 separate nights and a placebo on 2 separate nights. Subjects were awakened 2 hours into the sleep period during one triazolam and one placebo night for testing. Each of the drug conditions and wake-up nights were counterbalanced, and each drug night was separated by a 1-day washout period. (Continued)

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19. Abstract (continued)

Data included electroencephalography (EEG) activity, flight performance in the UH-60 simulator, subjective sleepiness, and cognitive performance. Each night of sleep also was recorded.

Analysis of the flight data indicated that aviators showed some decrements in flight performance in the morning following 8 hours of sleep with triazolam when compared to performance following 8 hours of sleep with placebo. Of the nine maneuvers flown, five had significant decreases in performance following a full night of sleep with triazolam. Most of these decrements occurred regardless of session; however, the morning session was more affected than the afternoon session on three of the maneuvers. The flight which occurred 2 hours postdose showed decrements in performance due to triazolam on only two of the maneuvers. This flight had worse performance on six of the maneuvers than the afternoon flight, regardless of the drug condition. The daytime EEG indicated more alertness following the nights with triazolam than following the nights with placebo. These results indicated that the sedative effects of triazolam were no longer evident 12 hours postdose. This effect was in agreement with the subjective sleepiness ratings in which subjects expressed less sleepiness during the late morning and early afternoon than after arising from sleep and just before bedtime. There were no differences in subjective sleepiness between triazolam and placebo. Subjects' sleep records indicated less awake time and stage 1 sleep following triazolam than following placebo, but sleep under placebo showed more slow wave sleep than under triazolam. During the interrupt nights, some subjects were slow to awaken under triazolam, and one subject had to be physically prompted before he awoke. However, triazolam helped aviators return to sleep faster than placebo, with significantly less awake time during the remainder of the sleep period. No effects such as daytime sleepiness and anxiety were reported by any of the subjects the next day following triazolam administration; however, two subjects were unable to recall portions of the midnight flight. In conclusion, the results of this study indicated that performance following 8 hours of sleep with triazolam is somewhat affected, but not to the extent that the aviator cannot maintain control of the aircraft. However, we cannot conclude from this study that performance in unusual situations will not be affected significantly by triazolam. We recommend that individuals who consider using triazolam to aid sleep be administered a test dose in a controlled situation to determine the length of time needed to awaken from sleep and if any adverse events such as amnesia will occur.

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All the subjects who willingly contributed their time to the study are greatly appreciated. Without their contribution, the study would have been impossible to complete.

Objectives

This study was designed to determine if an aviator who has taken a sleeping aid before bedtime could adequately perform his duties the following day after a full night of sleep. In addition, the project determined if an aviator who is awakened shortly after taking a sleeping aid could perform his required tasks. We hypothesized that a person who has taken a hypnotic in order to improve sleep quality may show more difficultly in performing a task immediately upon awakening than when awakened from nonhypnotic-induced sleep.

Military significance

During Operation Desert Shield/Desert Storm, flight surgeons in the field received a message establishing triazolam (Halcion®) as the sleeping aid of choice for aviation personnel unable to sleep under combat conditions. This drug was selected due to its availability and short half-life (Department of the Army, 1991). The message stated that a flight surgeon could prescribe triazolam (0.25 mg) to an aviator if all natural means of helping him sleep were ineffective. The aviator was grounded for 6 hours after administration of this hypnotic and was required to be under the flight surgeon's supervision. Since the end of Operation Desert Storm, the use of triazolam has been questioned by the aviation community because no controlled studies were conducted to determine the effects of this sleeping aid on the performance of aviators. Also, aviators and commanders have been concerned about the possibility of an aviator being administered a sleeping aid and a few hours later being called upon to fly his aircraft in an emergency situation. The possible consequences of such a situation are unknown; the person may experience grogginess and confusion upon awaking, and may even have trouble being roused from sleep at all. If too much sleep inertia is associated with hypnotic-induced sleep, it may not be feasible to administer a sleep aid in situations where emergencies may occur, such as during combat. In order to determine if triazolam should continue to be the drug of choice for wartime, research was needed to assess the advantages and disadvantages of this hypnotic for use in an aviation setting.

Background

When a person is roused from sleep, his proficiency in accomplishing a task may not be as good as his usual waking

performance. These performance deficits seen immediately upon awakening have been attributed to the effects of "sleep inertia" (Lubin et al., 1976), defined as a reduction in performance seen immediately upon awakening which lasts for several minutes until full wakefulness is achieved. Sleep inertia effects have been investigated for many years. Most investigators have found that performance is at its lowest within the first 5 minutes after awakening, with steady improvement thereafter until baseline levels are reached, usually within 15 to 30 minutes (Seminara and Shavelson, 1969). Sleep inertia is affected by a number of variables, including stage of sleep from which a person is awakened, the phase of his circadian cycle, and whether or not the sleep was pharmacologically induced.

In an investigation of performance after arousal at different times during the night, Wilkinson and Stretton (1971) found that reaction time was worse in the first half of the night than in the second. They attributed these findings to the individual's depth of sleep when he was awakened (most of stage 4 sleep occurs during the first half of the night and most of rapid eye movement [REM] sleep occurs during the second). These results were supported by Stones (1977) who found that performance on a memory task was worse when subjects were awakened from non-REM sleep than when awakened from REM sleep. Bonnet (1983) also found that short- and long-term memory were worse after awakening from stage 4 sleep than after awakening from stage 2 sleep. Additionally, in a study during which subjects slept during the afternoon and were aroused from stage 4 sleep, Webb and Agnew (1964) found that reaction time and performance on a serial response task declined significantly from baseline levels.

Differences in performance upon arousal from sleep also have been attributed to circadian fluctuations. Wilkinson and Stretton (1971) found that performance on a task requiring continuous concentration, as opposed to reaction time, was worse during the latter part of the night than during the earlier part of the night. The investigators attributed this difference to circadian fluctuations (performance during circadian troughs being worse than performance during circadian peaks). Circadian fluctuations also were found by Dinges, Orne, and Orne (1985) in a study in which people napped for 2 hours during circadian troughs and peaks over a 54-hour period. Performance immediately after awakening from naps during circadian troughs was impaired

compared to performance immediately after awakening from naps during circadian peaks.

Another factor which may degrade performance is the sleep interia induced by the use of an hypnotic. Whenever a pharmacological agent is used to initiate sleep, arousal thresholds are higher and sleep inertia is more prominent than when sleep occurs naturally. Research has shown that some people cannot awaken to stimuli, such as a tone or a fire alarm, during a drug-induced sleep (Johnson et al., 1987; Mendelson et al., 1988) and that performance on next-day tasks is disrupted after a drug-induced sleep (Church and Johnson, 1979; Walters and Lader, 1971). It is this effect of hypnotics which is of most concern to the aviation community.

Until several years ago, barbiturates were commonly administered to help initiate and maintain sleep. However, due to their "hangover" effects, their potential for dependency, the relatively high incidence of overdose fatalities, and their suppression of rapid eye movement (REM) sleep, the barbiturates were replaced by the benzodiazepines (Wheatley, 1981). Most of the popular benzodiazepines are successful at initiating and maintaining sleep during the night (Beary et al., 1984; Goetzke, Findeisen, and Welbers, 1983; Priest and Rizvi, 1976). However, there have been reports of early morning insomnia with some of the short-acting benzodiazepines (Kales et al., 1983) as well as rebound insomnia after their prolonged use (Kales, Scharf, and Kales, 1978; Kales et al., 1979; Morgan, Adam, and Oswald, 1984). Even with these findings, the benzodiazepines may be better and safer hypnotics than previous pharmacological interventions, especially when one compares the next day effects produced by the short-acting benzodiazepines to those of barbiturates.

The most desirable characteristics for a hypnotic are help in initiating and maintaining sleep, no disruption to normal sleep architecture, and no residual drug effects so the person may awaken in the morning refreshed and alert. This last point is especially important for aviators who generally are restricted from flying for several hours after drug administration. Ideally, any hypnotic administered to aviators should have no effect on their performance the following day. Additionally, the aviator should be able to be aroused from the drug-induced sleep if needed for emergencies even if this occurred before the completion of the scheduled sleep time and the drug has not cleared from the body.

Given the choices of sleeping aids available, the Army has chosen triazolam as its first line hypnotic during wartime (Department of the Army, 1991). Triazolam (Halcion®) is a short-acting benzodiazepine developed during the 1970s. Taken orally, it has a mean peak plasma time of 1.3 hours, with a mean half-life of about 2.3 hours (1.5 to 5.0 hours) (Eberts et al., 1981; Kroboth and Juhl, 1983). The recommended starting dosage for young- and middle-aged adults is 0.25 mg, and for older adults, 0.125 mg (Gillin, 1991; Kroboth and Juhl, 1983). Both laboratory and clinical trials have shown triazolam to be an effective hypnotic (Goetzke et al., 1983; Ogura et al., 1980; Vogel et al., 1975). Triazolam reduces sleep latency and the number of awakenings after sleep onset, increases total sleep time, increases the amount of stage 2 sleep, increases the latency of the first REM period without altering the overall percentage of REM sleep during the night, and does not significantly reduce slow wave sleep. Improved sleep has been reported in studies of both sleep-maintenance and sleep-onset insomniacs, as well as in normal, healthy sleepers. The quality of sleep has been reported to improve consistently with a 0.5 mg dose; however, some studies have shown that 0.25 mg is effective in improving sleep as well, although not as reliably as the larger dosage.

The popularity of triazolam comes from its short action -- it serves to initiate and maintain sleep, but has few hangover effects the next morning. Researchers have traced the timeline of triazolam's effects and have found that baseline levels of performance are reached between 8 and 10 hours postdose when the drug is taken at night (Balkin, et al., 1988; Bornstein, Watson, and Kaplan, 1985; Ogura et al., 1980; Roache and Griffiths, 1985; Spinweber and Johnson, 1982). Some performance decrements have been found in tests the next morning; however, these tests were administered less than 8 hours postdose (Walsh, Muehlbach, and Schweitzer, 1984).

Gorenstein and Gentil (1983) found that both triazolam (0.5 mg) and flurazepam (30 mg), a benzodiazepine with a half-life of about 2.3 hours, produced "hangover" effects in the morning as well as reduced motor performance. Roth and colleagues found that morning recall of a memory set was decreased following administration of either flurazepam (30 mg), lorazepam (4 mg), a benzodizepine with a half-life of about 12 hours, or triazolam (0.5 mg) (Roth et al., 1980). Their results indicated that the inability to recall information was due to memory consolidation

rather than failure of retrieval. However, Spinweber and Johnson (1982) did not find any significant performance decrements between a triazolam (0.5 mg) group and a placebo group. Tracing the time course of triazolam, these investigators found that performance was affected up to 5 hours postdose, but full recovery of performance was seen by 8 hours postdose.

Most of the research using triazolam has revealed no increase in sleepiness the day following the drug-induced sleep. In fact, Cohn (1984) found that insomniac patients reported less sleepiness during the early morning and late afternoon after taking triazolam (0.5 mg) than after taking lorazepam (2 mg). Ogura and colleagues supported these findings when comparing triazolam (0.25 and 0.5 mg), flurazepam (15 and 30 mg), nitrazepam (5 and 10 mg), and placebo (Ogura et al., 1980). Only slight residual effects in the morning were found after both doses of triazolam, but with fewer residual effects than flurazepam and nitrazepam.

However, investigators have found that, generally, arousal thresholds during a drug-induced sleep are higher than for normal sleep. In a study in which two doses of triazolam (0.25 mg and 0.5 mg) were administered to normal subjects, wakening to a smoke detector alarm was significantly slower during nights when subjects were administered the hypnotic than during placebo nights (Johnson et al., 1987). Additionally, the slowest responses were seen in the first stage 2 sleep period of the 0.5 mg night. Some subjects failed to awaken to the alarm when they were in slow wave sleep and had taken 0.5 mg triazolam. However, by morning, all subjects were easily awakened from sleep, regardless of the dose level received.

Although triazolam is beneficial at improving sleep with minimal hangover effects, some side effects have been seen in people using this medication. The most frequent side effects after consumption of triazolam are anterograde amnesia (loss of memory for events which happened after drug ingestion) and increased anxiety. Several researchers have found that subjects have difficulty recalling significant events which occurred during the night or that they performed poorly on memory tasks (Bixler et al., 1991; Roache and Griffiths, 1985; Roth et al., 1980). Increased anxiety is usually seen in insomniac patients taking the 0.5 mg dose (Kales et al., 1983; Morgan and Oswald, 1982; Morgan et al., 1984). Additionally, mixed results have been reported for rebound insomnia (increased difficulty in

sleeping without an hypnotic the night(s) following use of an hypnotic) and tolerance (repeated use of hypnotics which leads to a decreased effectiveness of the drug). Most researchers report rebound insomnia after at least 3 weeks of medication (Adam, Oswald, and Shapiro, 1984), but tolerance is not generally found even after long-term administration of the drug (Roth, Kramer, and Lutz, 1976; Vogel et al., 1975).

Even with the side effects associated with the use of triazolam, the Army has approved the use of this hypnotic during wartime. The fast rate of action as well as the relatively short half-life of triazolam are two of the major reasons. However, questions remain as to how aviators will perform their flight duties after taking this medication. Therefore, the present study addressed the issue of how triazolam affects the next-day performance of aviators after a full night of sleep as well as how triazolam affects flight performance of aviators who are awakened shortly after taking the drug. In order to fully assess the effects of triazolam, measures of flight performance, brain activity (EEG), cognitive performance, and subjective alertness were assessed various time after its administration.

Method

Subjects

The subjects were 10 male U.S. Army UH-60 helicopter pilots between the ages of 23 and 42 (mean = 29.7) and currently on flight status. Each subject was screened medically by a flight surgeon for current illness, sensitivity to hypnotics, and presence of significant heart abnormalities. This information was determined from a review of medical records and a face-to-face interview. Potential subjects were disqualified for any of the following reasons: current significant medical problems (including sleep abnormalities), use of tobacco products, current use of medications, and/or excessive use of caffeine (more than 5 cups of coffee or other caffeinated beverage per day). The subjects were instructed to abstain from drug and alcohol use for 48 hours prior to the beginning of the study and throughout the protocol.

Apparatus

Sleepiness measures

Subjective sleepiness was measured by the Stanford Sleepiness Scale (SSS). This questionnaire is a 7-point self-rating scale of sleepiness with response categories ranging from wide awake to almost asleep (Hoddes et al., 1973).

Cognitive measures

Selected subtests from the Walter Reed Army Institute of Research Performance Assessment Battery (WRAIR PAB), fully described by Thorne et al. (1985), were administered via microcomputer-based automated routines. The PAB system consisted of a Zenith 248* PC with a 20 megabyte internal hard drive, two floppy drives, an EGA graphics adapter, a Zenith color monitor, and a standard QWERTY keyboard. Stimuli were presented on a color monitor and responses were entered from the keyboard. The data obtained from each subtest were recorded automatically during each test session in a format which was later used to create the finalized data file for analysis on a Digital Equipment Corporation (DEC) VAX* 11/785 computer.

Electroencephalographic assessments

A Cadwell Spectrum 32* Neurometric analyzer was used to collect electroencephalographic (EEG) data from Fz, C3, Cz, C4, Pz, O1, and O2, referenced to linked mastoids using Grass* E5SH silver cup electrodes. The low filter was set at 0.53 Hz, the high filter was set at 70 Hz, and the 60 Hz notch filter was used. There was an eyes-closed/eyes-open spontaneous EEG, a visual P300, and an auditory middle latency response (MLR) recorded at each session; however, only the data from the resting EEG were analyzed. All test sessions were conducted in a dimly-illuminated, sound-attenuated chamber. Collected data were stored on optical disk for later analyses.

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*See list of manufacturers

Polysomnographic recordings

A Grass model 78D polygraph was used to collect electroencephalographic (EEG), electrooculographic (EOG), and electromyographic (EMG) data from the participants. EEGs were recorded from C3, C4, O1, and O2 referenced to the contralateral mastoids using Grass E5SH silver cup electrodes. The low filter was set at 1 Hz and the high filter was set at 35 Hz. EOGs were recorded from the outer canthus of each eye. The low filter was set at 0.3 Hz and the high filter was set at 10 Hz. EMG was recorded with submental electrodes, with a low filter setting of 10 Hz and a high filter setting of 90 Hz. The 60 Hz notch filter was not used. Collected data were recorded at a chart speed of 10 mm per second on standard polygraph paper for later scoring.

Flight performance

All simulator flights were conducted on site at the U.S. Army Aeromedical Research Laboratory (USAARL) facility at Fort Rucker, Alabama, using the USAARL UH-60 research flight simulator. This motion-base system includes an operational crew station, computer-generated visual display (set for standard daytime flight), environmental conditioning (set at a constant cockpit temperature of 72 degrees Fahrenheit and a humidity of 70%), and a multi-channel data acquisition system.

Flight data were acquired on a DEC VAX 11/780 interfaced to a Perkin-Elmer* digital computer which controls the UH-60 flight simulator. This system is capable of monitoring any aspect of simulator control, from heading, air speed, and altitude, to global positioning system (GPS) readouts, switch positions, and operator console inputs. However, for the purposes of this investigation, only 17 channels of data were monitored.

The acquired data points initially were stored on the DEC VAX 11/780, but at the end of each flight, they were transferred to the main USAARL computer, a DEC VAX 11/785. Flight performance scores, including root mean square (RMS) errors, were derived using specialized software routines developed in the Laboratory (Jones and Higdon, 1991). These data were subsequently examined with standard statistical procedures (described later).

The flight performance evaluations required subjects to perform the profile described in Table 1. Note that there were

three parts to each flight. The first part consisted of tactical navigation in which the subject was required to use visual cues, doppler information, and time information to correctly navigate the course. The second part consisted of nontactical, upper-airwork in which the subject was required to perform precision maneuvers based upon instrument information. This part of the flight was also divided into two groups; the first group of maneuvers was flown with the automatic flight control system (AFCS) trim engaged, and the second group was flown with the AFCS trim turned off, adding a level of difficulty to the control of the aircraft. The third part consisted of nap-of-the-earth (NOE) flight in which the subject was required to follow a leadship during flight at altitudes close to the earth for a set amount of time. The same sequence of maneuvers was used for every subject during each of the training flights. These maneuvers are of the type typically flown in a UH-60 aircraft, and they are fully described in the Aircrew Training Manual (ATM).

The entire profile lasted approximately 1 hour, and during each profile, performance was measured using the simulator's computerized performance monitoring system which was described earlier. Each maneuver was scored for parameters such as airspeed, altitude, slip, roll, etc. Each maneuver along with the parameters measured are listed in Table 2. During each flight, the console operator, a UH-60 pilot, was present to instruct the subject and ensure the proper sequencing of all flight maneuvers. In addition, the console operator marked the beginning and ending point of each individual maneuver for the purpose of delimiting subsequent computer scoring. He also informed the subject about the maneuver to be flown and marked the start point of the maneuver when the subject was instructed to initiate that maneuver.

Procedure

Each subject was tested over a period of 10 days. The first day served as a screening day, 2 days were training days, 2 days were active drug days (0.25 mg triazolam), 2 days were placebo days, and a control day separated each drug/placebo day. The 4 drug days were counterbalanced and the conditions were double-blind. Test sessions for the simulator flights normally occurred at 0600 and 1300, and the cognitive and electrophysiological tests occurred at 0900 and 1600. In addition, 1 drug night and 1 placebo night (with simulator flights at 0030 and 1300) were used to determine the effects of the hypnotic on flight

performance soon after dose administration. These test days (sleep interruption days) were also counterbalanced over the test period, and the subject was not aware of which nights he would be awakened early.

Each subject was instructed to report to the Laboratory on Monday afternoon. At that time, the principal investigator fully explained the details of the study, the subject signed the informed consent, and the medical monitor screened the subject for medical acceptability into the study. A copy of the informed consent is contained in Appendix A. At 2100, electrodes were attached to the subject's scalp. Approximately 15 minutes before bedtime, the subject was escorted to his bedroom, electrodes were checked, and lights out occurred at 2200. This first night served as an acclimation period, and no physiological recordings were made. The subject was awakened at 0530 the next morning (Tuesday). Tuesday and Wednesday served as training days in the simulator and on the cognitive tests. Tuesday night served as baseline recording night for the sleep measures. At 2100, the electrodes were checked and repaired as necessary and the subject retired to his sleeping quarters. Lights out was at 2200. Physiological recordings of EEG, EMG, and EOG were made continuously during the sleep period. The subject was awakened at 0530 on Wednesday morning to continue training on the various tasks. The first administration of either drug or placebo was Wednesday night at 2155, just before lights out at 2200. Test days began on Thursday with the subject being awakened at 0530.

The simulator flights occurred twice per day, at 0600 and 1300 after the full night of sleep and at 0030 and 1300 after the interrupted night of sleep. Prior to actual testing, subjects received four training sessions on the flight profile presented in Table 2. During all flights, subjects were instructed when to begin each of the maneuvers, and the console operator marked the start and stop point of each. The entire flight profile took approximately 1 hour to complete.

Table 1.
Flight profile.

Maneuver	Description
1. Low hover	Maintain heading 150°, altitude 10 ft
2. Low hover turn	Heading from 150° to 330° while holding altitude of 10 ft above ground level
3. High hover	Maintain heading 330°, altitude 40 ft
4. High hover turn	Heading from 330° to 150°, while holding altitude of 40 ft above ground level
5. Navigate to checkpoint 1	Maintain GPS heading within 10° Maintain 700 ft MSL within 100 ft Arrive at checkpoint in 3 min
6. Navigate to checkpoint 2	Maintain GPS heading within 10° Maintain 600 ft MSL within 100 ft Arrive at checkpoint in 2 min
7. Navigate to checkpoint 3	Maintain GPS heading within 10° Maintain 600 ft MSL within 100 ft Arrive at checkpoint in 5 min
8. Navigate to checkpoint 4	Maintain GPS heading within 10° Maintain 600 ft MSL within 100 ft Arrive at checkpoint in 2 min
9. Navigate to checkpoint 5	Maintain GPS heading within 10° Maintain 700 ft MSL within 100 ft Arrive at checkpoint in 4 min
10. Transition	Establish heading 360°, airspeed 120 k, and altitude 2000 ft MSL for 1 min
11. Straight & level	Maintain the above parameters 1 min
12. Left standard rate turn	Perform 360° left standard rate turn maintaining airspeed and altitude
13. Straight & level	Maintain heading 360°, airspeed 120 k, and altitude 2000 ft MSL for 1 min
14. Climb	Climb from 2000 to 2500 ft while maintaining heading and airspeed (1 min)
15. Right standard rate turn	Perform 180° right standard rate turn maintaining airspeed and altitude

Table 1 (continued)

Maneuver	Description
16. Straight & level	Maintain heading 180°, airspeed 120 k, and altitude 2500 ft MSL 1 for 1 min
17. Right standard rate turn	Perform 180° right standard rate turn maintaining airspeed and altitude
18. Climb	Climb from 2500 to 3500 ft while maintaining heading and airspeed
19. TURN AFCS OFF	----------
20. Descend	Descend from 3500 to 3000 ft while maintaining heading and airspeed
21. Left descending turn	Perform 180° left standard rate turn while descending turn from 3000 to 2500 ft maintaining airspeed
22. Descent	Descend from 2500 to 2000 ft while maintaining heading and airspeed
23. Left standard rate turn	Perform 180° left standard rate turn maintaining altitude and airspeed
24. Straight & level	Maintain heading 360°, airspeed 120 k, altitude 2000 ft for 2 min
25. Right standard rate turn	Perform 360° right standard rate turn while maintaining altitude and airspeed
26. Descent	Descend from 2000 to 1000 ft MSL maintaining heading and airspeed
27. TURN AFCS ON - MOVE TO COORDINATES	
28. Terrain flight Approach to LZ	Maintain airspeed until approach angle intercept Touch down in Y zero ground speed
29. Formation flight takeoff (Staggered left)	Maintain 3 rotor disk separation at 30° angle Maintain altitude and airspeed
30. Formation flight (staggered left)	Maintain 3 rotor disk separation at 30° angle Maintain altitude and airspeed
31. Formation flight (trail)	Maintain 3 rotor disk separation behind lead ship; Maintain altitude and airspeed
32. Formation flight approach (trail)	Maintain 3 rotor disk separation behind lead ship; touch down with lead

Table 2.
Maneuvers with parameters scored.

Maneuver	Parameters	Ideal Values
AFCS ON		
Straight and level	Heading	360 degrees
	Altitude	2000 feet MSL
	Airspeed	120 knots
	Roll	0 degrees
Left Standard Rate Turn	Turn rate	3 degrees/second
	Altitude	2000 feet MSL
	Airspeed	120 knots
	Slip	0 ball position
	Roll	20 degrees
Straight and level	Heading	360 degrees
	Altitude	2000 feet MSL
	Airspeed	120 knots
	Roll	0 degrees
Climb	Heading	360 degrees
	Airspeed	120 knots
	Slip	0 ball position
	Roll	0 degrees
	Rate of Climb	500 feet/minute
Right Standard Rate Turn	Turn rate	3 degrees/second
	Altitude	2000 feet MSL
	Airspeed	120 knots
	Slip	0 ball position
	Roll	20 degrees
Straight and level	Heading	180 degrees
	Altitude	2500 feet MSL
	Airspeed	120 knots
	Roll	0 degrees
Right Standard Rate Turn	Turn rate	3 degrees/second
	Altitude	2000 feet MSL
	Airspeed	120 knots
	Slip	0 ball position
	Roll	20 degrees
Climb	Heading	360 degrees
	Airspeed	120 knots
	Slip	0 ball position
	Roll	0 degrees
	Rate of Climb	500 feet/minute

Table 2 (continued)

Maneuver	Parameters	Ideal Values
AFSC OFF		
Descent	Heading	360 degrees
	Airspeed	120 knots
	Slip	0 ball position
	Roll	0 degrees
	Rate of Descent	500 feet/minute
Left Descending Turn	Turn Rate	3 degrees/second
	Airspeed	120 knots
	Slip	0 ball position
	Roll	20 degrees
	Rate of Descent	500 feet/minute
Descent	Heading	180 degrees
	Airspeed	120 knots
	Slip	0 ball position
	Roll	0 degrees
	Rate of Descent	500 feet/minute
Left Standard Rate Turn	Turn Rate	3 degrees/second
	Altitude	2000 feet MSL
	Airspeed	120 knots
	Slip	0 ball position
	Roll	20 degrees
Straight and level	Heading	360 degrees
	Altitude	2000 feet MSL
	Airspeed	120 knots
	Roll	0 degrees
Right Standard Rate Turn	Turn Rate	3 degrees/second
	Altitude	2000 feet MSL
	Airspeed	120 knots
	Slip	0 ball position
	Roll	20 degrees
Descent	Heading	360 degrees
	Airspeed	120 knots
	Slip	0 ball position
	Roll	0 degrees
	Rate of Descent	500 feet/minute

During the sleep interruption test days, the subject was awakened at 2400 by a tone presented through the intercom at a rate of once per second until he responded by pressing a button located next to his bed. The time required to awaken the subject was recorded on the polygraph by a mark when the tones began and a mark when the subject pressed the response button. The simulator flight was at 0030. After the flight, the subject returned to bed at 0200. He was allowed to sleep until 0730 in order to maintain the same amount of time spent in bed each night (7.5 hours).

The electroencephalographic (EEG) assessments were conducted at 0900 and 1600. Each EEG session lasted approximately 30 minutes and began with a check of electrode impedances to ensure that they were all 5000 Ohms or less. Any impedance problems were corrected by rotating a blunted needle gently inside the problem electrode until an adequate signal was obtained. Once all impedances were within an acceptable range, the subject was instructed to sit quietly with his eyes opened for 1 minute followed by 1 minute of eyes closed while data were recorded.

The PAB was administered at 0930 and 1630. Prior to the first actual test session on Thursday, subjects were trained on the exact procedure to be used in completing each subtest via an interactive sequence with an investigator. Subjects were told to emphasize both speed and accuracy of performance. Initially, they were encouraged to ask for help at any point during the instructional period, but as training progressed, the subjects were expected to function autonomously. Six training sessions were administered over the first 2 days of the study, with baseline measures taken on Wednesday. The specific subtests were as follows:

1. Six-letter search (MAST-6): The subject was presented with 6 letters at the top of the screen and a row of 20 letters at the bottom of the screen. He determined if the top row of letters was contained in the bottom row of letters. If every letter was displayed in the bottom row (in any order), the subject pressed "S." If any letter from the top row was missing in the bottom row, the subject responded by pressing "D."

2. Logical reasoning: The letter pair "A/B" or "B/A" was presented in the top of the display with a logical statement describing the letters presented in the bottom of the display. The subject determined if the statement correctly described the

letters. If so, the subject responded by pressing the letter "S"; if the statements did not correctly describe the letters, the subject pressed the letter "D."

3. Serial addition/subtraction: Two numbers were displayed in sequence, followed by either a "+" or a "-" flashed after the numbers. The subject performed the indicated operation, either addition or subtraction. If the answer was less than zero, the subject added 10 to the number and input the new answer; if the answer was greater than 9, the subject subtracted 10 from the answer and input the new answer. Each number for input was between 0 and 9, inclusive.

The polysomnographic recordings were made while subjects slept in a darkened, private bedroom. At the beginning of each night, the subject was escorted into his bedroom where the electrodes were plugged into the preamplifier and signals were checked for integrity. After the system was verified, the lights were turned out and the subject slept while electrophysiological data were recorded. After each subject had been tested, the polysomnographic data were scored manually by experienced sleep scorers who were blind to drug condition. The guidelines set forth by Rechtschaffen and Kales (1968) were followed.

The SSS was administered 20 minutes after waking (both at midnight and at the end of the sleep periods), 10 minutes before each simulator flight, during each cognitive testing session, and 15 minutes before lights out. Subjects were completely trained on the procedures for this questionnaire during the training/baseline period. The testing days and the schedule are shown in Table 3.

Results

Sleepiness scale

The questionnaire data indicating participants' subjective impressions about their level of sleepiness were analyzed with two separate repeated measures analysis of variance (ANOVA) procedures. A 2 (drug day) X 5 (session) repeated measures ANOVA was used to analyze the full night of sleep and a 2 (drug day) X 6 (session) repeated measures ANOVA was used to analyze the interrupted night of sleep. Although the data are ordinal level of measurement, ANOVA is robust with regard to violations of the

Table 3.
Testing Schedule

Time	Mon	Tue *Trng*	Wed *Bsln*	Thu *Test*	Fri *Control*	Sat *Test*	Sun *Control*	Mon *Test*	Tue *Control*	Wed *Test*	Thu *Control*
00-01								Wake-up SSS/SIM		Wake-up SSS/SIM	
01-02								SIM		SIM	
02-03								LO		LO	
03-04											
04-05											
05-06		Wake-up	Wake-up	Wake-up	Wake-up	Wake-up	Wake-up		Wake-up		Wake-up
06-07		SSS/SIM	SSS/SIM	SSS/SIM	SSS/SIM	SSS/SIM	SSS/SIM		SSS/SIM		SSS/SIM
07-08		Brkft	Brkft	Brkft	Brkft	Brkft	Brkft	Wake-up	Brkft	Wake-up	Brkft
08-09		FREE	FREE	FREE	FREE	FREE	FREE	SSS Brkft	FREE	SSS Brkft	FREE
09-10		EEG/EP SSS/PAB	EEG/EP SSS/PAB	EEG/EP SSS/PAB	EEG/EP SSS/PAB	EEG/EP SSS/PAB	EEG/EP SSS/PAB	EEG/EP SSS/PAB	EEG/EP SSS/PAB	EEG/EP SSS/PAB	EEG/EP SSS/PAB
10-11		FREE	FREE	FREE	FREE	FREE	FREE	FREE	FREE	FREE	FREE
11-12		Lunch	Lunch	Lunch	Lunch	Lunch	Lunch	Lunch	Lunch	Lunch	Lunch
12-13		FREE	FREE	FREE	FREE	FREE	FREE	FREE	FREE	FREE	FREE
13-14		SSS/SIM	SSS/SIM	SSS/SIM	SSS/SIM	SSS/SIM	SSS/SIM	SSS/SIM	SSS/SIM	SSS/SIM	SSS/SIM
14-15	Arrive	FREE	FREE	FREE	FREE	FREE	FREE	FREE	FREE	FREE	FREE
15-16		FREE	FREE	FREE	FREE	FREE	FREE	FREE	FREE	FREE	FREE
16-17	Consent	EEG/EP SSS/PAB	EEG/EP SSS/PAB	EEG/EP SSS/PAB	EEG/EP SSS/PAB	EEG/EP SSS/PAB	EEG/EP SSS/PAB	EEG/EP SSS/PAB	EEG/EP SSS/PAB	EEG/EP SSS/PAB	EEG/EP SSS/PAB
17-18	Med	FREE	FREE	FREE	FREE	FREE	FREE	FREE	FREE	FREE	Debrief Release
18-19	Dinner	Dinner	Dinner	Dinner	Dinner	Dinner	Dinner	Dinner	Dinner	Dinner	
19-20	FREE	FREE	FREE	FREE	FREE	FREE	FREE	FREE	FREE	FREE	
20-21	Elec Hook-up	Elec Rep	Elec Rep	Elec Rep	Elec Rep	Elec Rep	Elec Rep	Elec Rep	Elec Rep	Elec Rep	
21-22		SSS	SSS/DRG	SSS	SSS/DRG	SSS	SSS/DRG	SSS	SSS/DRG	SSS	
22-23	LO	LO	LO	LO	LO	LO	LO	LO	LO	LO	
23-24											

DRG = Triazolam or placebo

interval-level measurement assumption (Tabachnick and Fidell, 1983).

The analysis of the full night of sleep indicated a significant effect for session ($F(4,36)=5.33$, $p=.0018$). Contrasts of the means indicated that the subjects expressed significantly more sleepiness immediately upon arising (0550) and at 0900 than at 1250 or 1600 ($p<.05$). They expressed less sleepiness at 1250 and 1600 than at 2145, 15 minutes before their scheduled bedtime. (See Figure 1)

The analysis of the interrupted night of sleep also indicated a significant effect for session ($F(5,45)=9.71$, $p<.0001$). Contrasts of the means indicated that the subjects expressed significantly more sleepiness upon arising at midnight than at any of the other sessions ($p<.05$). In addition, they also expressed more sleepiness at 0750 (after awakening in the morning) and at 2145 (15 minutes before lights out) than at 1250. These results are shown in Figure 1.

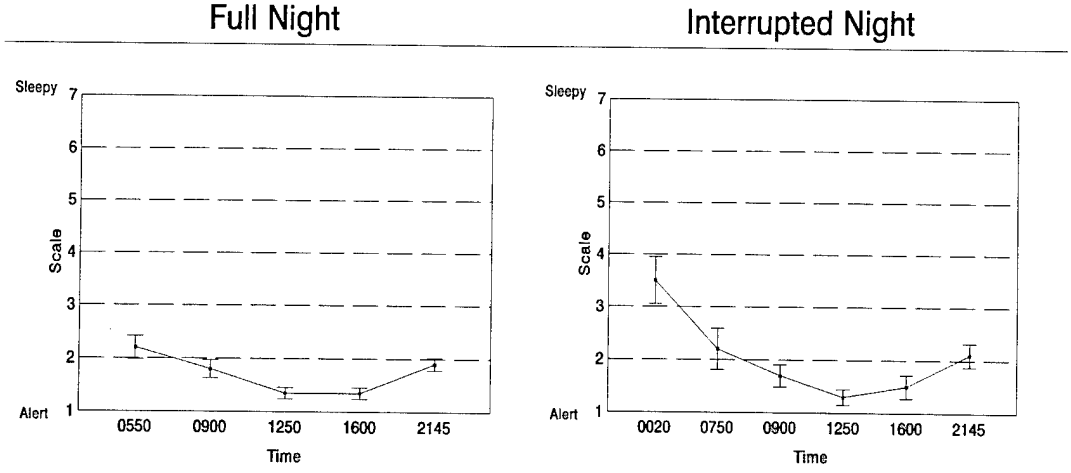

Figure 1. SSS scores main effect for session for both full and interrupted nights of sleep.

Performance Assessment Battery

Each of the three tests were analyzed for percent correct, reaction time, and throughput (a derived score which measures number of correct responses per minute). These variables were analyzed using a 2 (drug day) X 2 (wake-up condition) X 2 (session) repeated measures ANOVA. The percent correct variable was transformed using the 2*arcsin(sqrt(x)) transformation as suggested by Winer (1971). Analysis of simple effects and contrasts were used for follow-up analyses when appropriate.

Six-letter search

The analysis of the six-letter search test (MAST-6) indicated a main effect for session (morning, 0930, vs afternoon, 1630) on reaction time ($F(1,9)=18.82$, $p=.0019$). The average reaction time from the morning session was longer than the average reaction time from the afternoon session (9.6 seconds vs 8.8 seconds, respectively). There was a similar tendency for throughput, but this did not reach statistical significance ($p=.07$). There was no drug or wake-up condition effect, nor were there any interactions among any of the variables.

Logical reasoning

The analysis of the logical reasoning test also indicated a session effect for both reaction time ($F(1,9)=9.79$, $p=.0121$) and throughput ($F(1,9)=8.97$, $p=.0151$). The reaction times in the morning were again slower than in the afternoon (3.26 and 3.05, respectively). There also were fewer number correct responses per minute in the morning than in the afternoon (.34 vs .36, respectively). There was a tendency for reaction time to be longer after the interrupted night of sleep than after the full night of sleep, but this did not reach statistical significance ($p=.06$). There also was a nonsignificant tendency ($p=.08$) for percent correct to be different after the 2 drug days with the triazolam day showing fewer correct responses than the placebo day (96% vs 98%). There were no significant interactions among any of the variables.

Serial addition/subtraction

The analysis of the serial addition/subtraction test did not show any main effects or interactions for any of the factors.

Electroencephalography assessments

Resting EEG data were analyzed in a four-way repeated measures analysis of variance: drug (triazolam and placebo), wake-up condition (sleep and interrupted), session (morning, 0900, and afternoon, 1600), and eyes (open and closed). The amount of delta (1.5-3.0 Hz), theta (3.0-8.0 Hz), alpha (8.0-13.0 Hz), and beta (12.5-20 Hz) activity, in terms of relative power, at four midline electrode locations (Fz, Cz, Pz, and Oz) and four hemisphere electrodes (C3, C4, O1, and O2) were analyzed.

Beta activity

Analysis of the beta activity indicated a three-way interaction among drug, session, and eyes at electrode sites Fz ($F(1,9)=6.36$, $p=.0326$), Cz ($F(1,9)=5.07$, $p=.0508$), and Pz ($F(1,9)=7.30$, $p=.0243$). Further analyses indicated only a difference between eyes closed and eyes open at sites Cz and Fz. However, at site Pz, analyses indicated that, during eyes open following triazolam in the morning session, there was less beta activity than in the afternoon session ($p<.05$). This effect was not significant following placebo. Also, during the morning session at eyes closed, there was less beta activity under placebo than under triazolam ($p<.05$), but no differences occurred during the afternoon session. Figure 2 shows these effects.

A two-way interaction occurred between drug and session at electrode site Pz ($F(1,9)=5.75$, $p=.0401$). Post hoc analyses indicated more beta activity during the afternoon session than during the morning session following placebo ($p<.05$), but not following triazolam. Figure 3 shows this effect.

A main effect for session occurred at electrode site Pz ($F(1,9)=5.00$, $p=.0522$), with less beta activity during the morning session than during the afternoon session. A main effect also occurred for eyes open/closed at electrode sites C3 ($F(1,9)=7.70$, $p=.0216$), C4 ($F(1,9)=7.70$, $p=.0216$), O1 ($F(1,9)=10.86$, $p=.0093$), O2 ($F(1,9)=18.82$, $p=.0019$), Fz ($F(1,9)=9.44$, $p=.0133$), Cz ($F(1,9)=8.57$), Pz ($F(1,9)=14.12$, $p=.0045$) and Oz ($F(1,9)=14.60$, $p=.0041$). Inspection of the means at each of these sites indicated more beta activity during eyes closed than during eyes open.

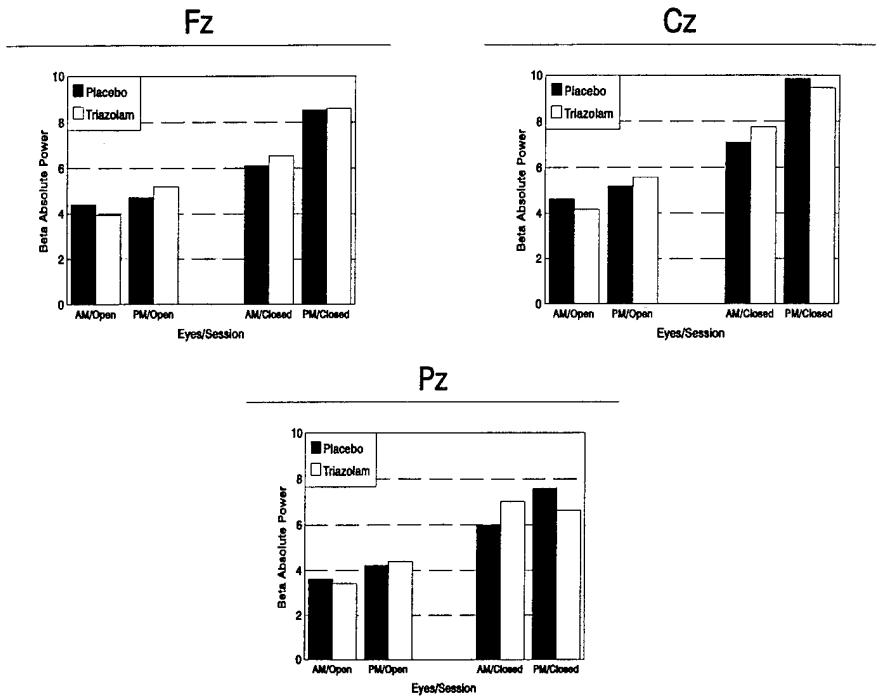

Figure 2. Beta activity interaction among drug day, session, and eyes for electrode sites Fz, Cz, and Pz.

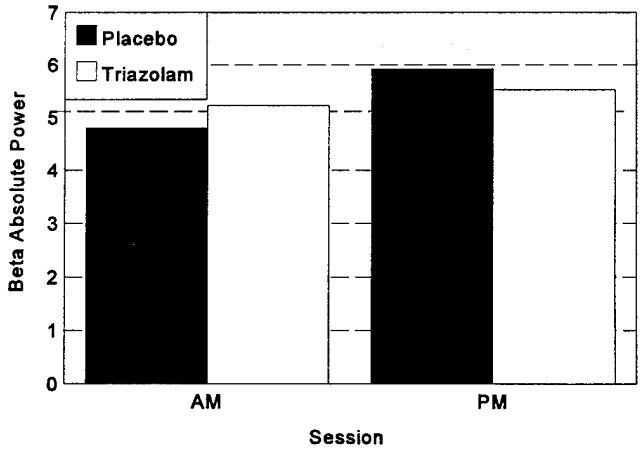

Figure 3. Beta activity interaction between drug day and session for electrode site Pz.

Alpha activity

Analysis of alpha activity indicated a two-way interaction between drug day and eyes at electrode site Pz ($F(1,9)=5.14$, $p=.0496$). Post hoc analyses indicated less alpha activity during eyes open than during eyes closed after both placebo and triazolam ($p<.05$). (See Figure 4) There also was a tendency for more alpha activity to occur during eyes closed following placebo than following triazolam, but this effect did not reach statistical significance ($p=.06$).

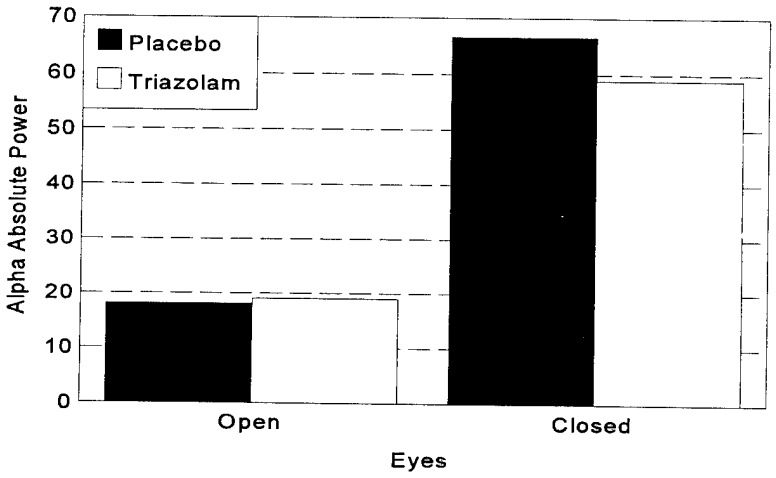

Figure 4. Alpha activity interaction between drug day and eyes at electrode site Pz.

A main effect for drug day occurred at electrode sites O1 ($F(1,9)=9.11$, $p=.0145$) and Oz ($F(1,9)=12.60$, $p=.0062$) because there was more alpha activity following placebo than following triazolam (O1: 42.71 and 36.73; Oz: 43.86 and 39.63, respectively). A main effect also occurred for eyes at electrode sites C3 ($F(1,9)=8.70$, $p=.0163$), C4 ($F(1,9)=8.35$, $p=.0179$), O1 ($F(1,9)=13.37$, $p=.0053$), O2 ($F(1,9)=13.46$, $p=.0052$), Fz ($F(1,9)=10.89$, $p=.0092$), Cz ($F(1,9)=9.58$, $p=.0128$), Pz ($F(1,9)=9.31$, $p=.0138$), and Oz ($F(1,9)=13.29$, $p=.0054$). At every electrode site, there was more alpha activity during eyes closed than during eyes open.

Theta activity

An analysis of theta activity indicated a four-way interaction among drug day, wakeup condition, session, and eyes at electrode site Pz ($F(1,9)=7.09$, $p=.0260$). Further investigation indicated that during the afternoon session with eyes closed following the interrupted night of sleep, there was more theta activity under placebo than under triazolam ($p<.05$).

A two-way interaction between session and eyes also occurred at electrode site Pz ($F(1,9)=8.79$, $p=.0158$). Post hoc analyses indicated more theta activity at the afternoon session than at the morning session during eyes open ($p<.05$), but not during eyes closed. (See Figure 5) A similar effect occurred at electrode sites C3 and Cz, but these were not statistically significant ($p=.08$ and .07, respectively).

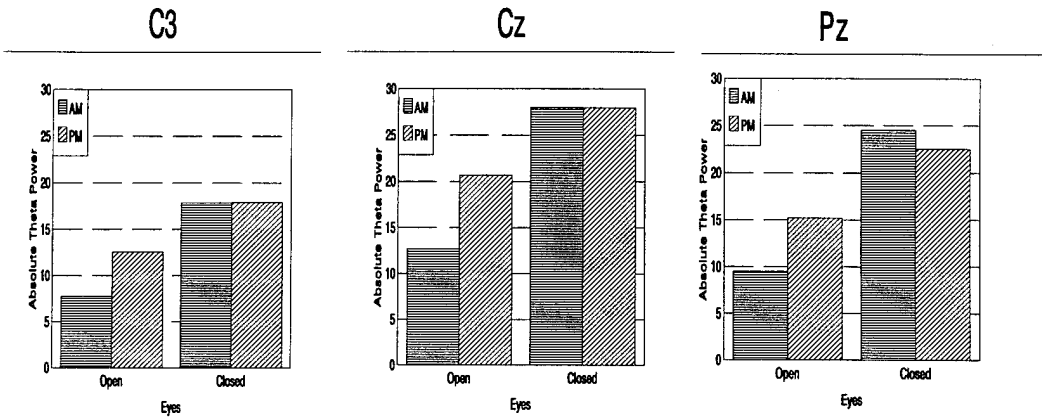

Figure 5. Theta activity interaction between session and eyes at electrode sites C3, Cz, and Pz.

A main effect for drug day occurred at electrode sites C3 ($F(1,9)=9.95$, $p=.0117$), C4 ($F(1,9)=5.65$, $p=.0415$), Cz ($F(1,9)=8.33$, $p=.0180$), and Pz ($F(1,9)=8.84$, $p=.0156$), with more

theta activity following placebo than following triazolam. A similar effect occurred at electrode site Fz, but this effect did not reach statistical significance (p=.06). A main effect for eyes occurred at electrode sites C3 ($F(1,9)=7.61$, p=.0222), C4 ($F(1,9)=11.42$, p=.0081), O1 ($F(1,9)=7.88$, p=.0204), O2 ($F(1,9)=9.07$, p=.0147), Fz ($F(1,9)=10.73$, p=.0096), Cz ($F(1,9)=10.50$, p=.0102), Pz ($F(1,9)=8.92$, p=.0153), and Oz ($F(1,9)=8.34$, p=.0180). More theta activity occurred during eyes closed than during eyes open at every electrode site.

Delta activity

Analysis of delta activity indicated a two-way interaction between wake-up condition and session at electrode site C3 ($F(1,9)=5.46$, p=.0443). Further analyses did not show any statistically significant differences between any of the means. However, there was a tendency for more delta activity to occur during the afternoon session than during the morning session after the interrupted night of sleep, but not after the full night of sleep (p=.08). Another two-way interaction occurred between session and eyes at electrode site O2 ($F(1,9)=10.19$, p=.0110). Again, no significant differences between the means occurred, but there was a tendency for more delta activity during eyes closed than during eyes open at the morning session (p=.07), but not at the afternoon session.

A main effect for drug day occurred at electrode sites C4 ($F(1,9)=6.44$, p=.0318) and Pz ($F(1,9)=9.04$, p=.0148). There was more delta activity following placebo than following triazolam. A similar effect occurred at electrode site C3, but this was not statistically significant (p=.07). A main effect also occurred for eyes at electrode site C4 ($F(1,9)=5.79$, p=.0395), Fz ($F(1,9)=7.61$, p=.0221), and Cz ($F(1,9)=5.19$, p=.0487). More delta activity occurred during eyes closed than during eyes open.

Polysomnographic analysis

The data recorded from nights 2 through 10 were scored in 30-second epochs for sleep stage according to standard procedures (Rechtschaffen and Kales, 1968). Only the four drug nights were compared in the statistical analysis. The variables of interest included time of sleep onset (from lights out to the first full minute of stage 2), percent of total sleep time in stages 1, 2, 3, 4, REM, and awake after sleep onset, and the number of minutes scored as movement. Each variable was analyzed using a 2 (drug

day) X 2 (wake-up condition) repeated measures analysis of variance. Percent data were transformed using 2*arcsin(sqrt X) as suggested by Winer (1971). Simple effects and contrasts were used to follow up significant interactions. Main effects were analyzed, when appropriate, by contrasts.

The results of the analysis indicated no interactions between drug day and wake-up condition for any of the stages of sleep ($p>.05$). However, there were main effects for drug day on percent stage 1 ($F(1,9)=23.82$, $p=.0009$), percent stage 2 ($F(1,9)=17.13$, $p=.0025$), percent stage 3 ($F(1,9)=5.74$, $p=.0401$), and percent awake ($F(1,9)=12.75$, $p=.0060$). There was more stage 2 sleep after triazolam than after placebo, but less stage 1, stage 3, and awake time after triazolam than after placebo, as can be seen in Figure 6.

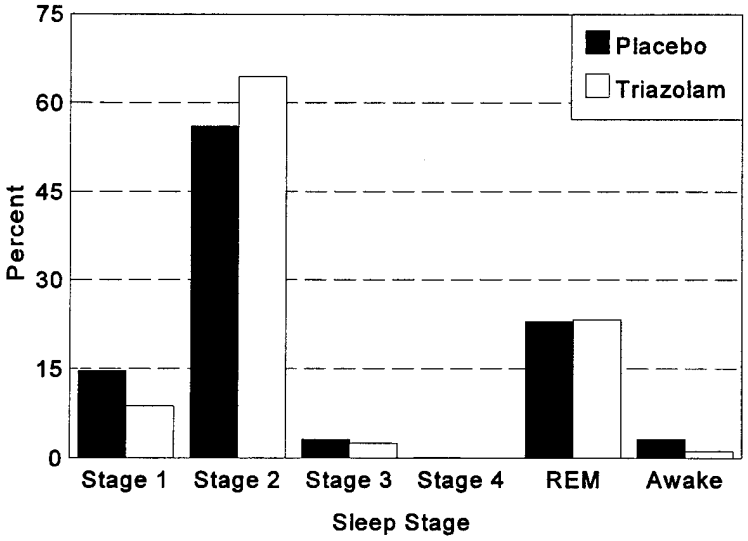

Figure 6. Percent of time spent in each stage of sleep by drug condition.

There also was a main effect for wake-up condition on percent stage 2 ($F(1,9)=29.64$, $p=.0004$), percent REM ($F(1,9)=6.13$, $p=.0353$), percent time awake after sleep onset ($F(1,9)=23.65$, $p=.0009$), and minutes scored as movement ($F(1,9)=4.97$, $p=.0528$). There was more stage 2 and movement on the full night of sleep than on the interrupted night, and less REM sleep and awake time after sleep onset on the full night of sleep than on the interrupted night. (See Figure 7)

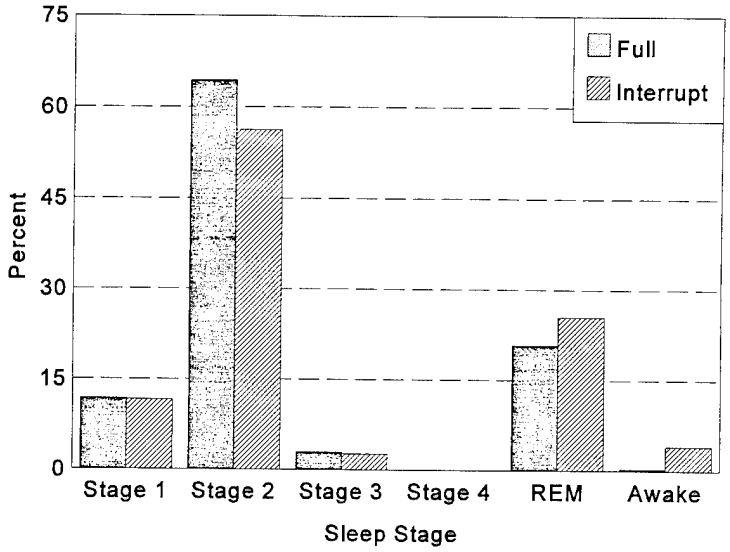

Figure 7. Percent time spent in each stage by full and interrupted nights of sleep.

A two-way ANOVA to determine whether the drug affected the amount of time to respond to the morning wakeup signal at 0530 and 0730 was conducted using drug day and wakeup condition as factors. No interaction occurred between the two factors, nor was a main effect evident for either factor. There was a tendency towards slightly longer wake-up times on triazolam versus the placebo mornings (7.70 seconds and 5.93 seconds, respectively), but these were not statistically significant ($p=.08$).

A one-way ANOVA was conducted on the number of seconds taken to respond to the midnight wake-up signal. No drug effect was found. However, a wide range of responses occurred during the triazolam night, giving a very large variance which was responsible for the nonsignificant F value ($F(1,9)=1.63$, $p=.2337$). One subject did not awaken until the technician went into the room and called him several times. The wake-up signal was given for 363 seconds before the technician intervened. The mean number of seconds to respond to the wakeup signal was 53.80 ($sd=110.52$) for the triazolam night and 8.4 ($sd=4.87$) for the placebo night.

Another variable submitted to a one-way ANOVA was sleep onset time upon returning to bed after the midnight simulator flight. A main effect for drug day was found ($F(1,9)=6.98$,

p=.0268); the means indicated that subjects were able to return to sleep faster on their triazolam night than on their placebo night (13.30 minutes versus 33.60 minutes, respectively).

Flight performance

Drug-related changes in flight performance were determined using two separate BMDP4V* repeated measures ANOVA; one analysis was conducted for the full night of sleep and one analysis was conducted for the interrupted night of sleep since these two conditions were not comparable in terms of the times at which the morning flights occurred (0030 versus 0600). The factors for both analyses included drug day (triazolam and placebo) and session (morning and afternoon). When a maneuver occurred more than once in the flight profile, iteration (another factor) was added to the analysis. This was the case for every maneuver except the left descending turn which occurred only once in the flight profile. Significant interactions were followed up with simple effects and contrasts, and main effects were analyzed using contrasts to determine where the means were significantly different.

Straight hovers

Two ANOVAs were used to determine the ability of subjects to maintain control of heading and altitude during both 10- and 40-foot hovers. The analysis of the full night of sleep indicated a two-way interaction between session and iteration for altitude control ($F(1,9)=7.78$, $p=.0211$). Further analyses indicated that during the 40-foot hover, performance during the morning session (0600) was worse than performance during the afternoon session ($p<.05$). This effect did not occur for the 10-foot hover. In addition, the morning performance on the 40-foot hover was worse than the morning performance on the 10-foot hover ($p<.05$) while there were no differences between the two in the afternoon. These effects are shown in Figure 8.

A main effect for iteration was revealed for the altitude measure ($F(1,9)=7.84$, $p=.0207$). The performance on the 40-foot hover was worse than the performance on the 10-foot hover (30.48 and 29.60, respectively).

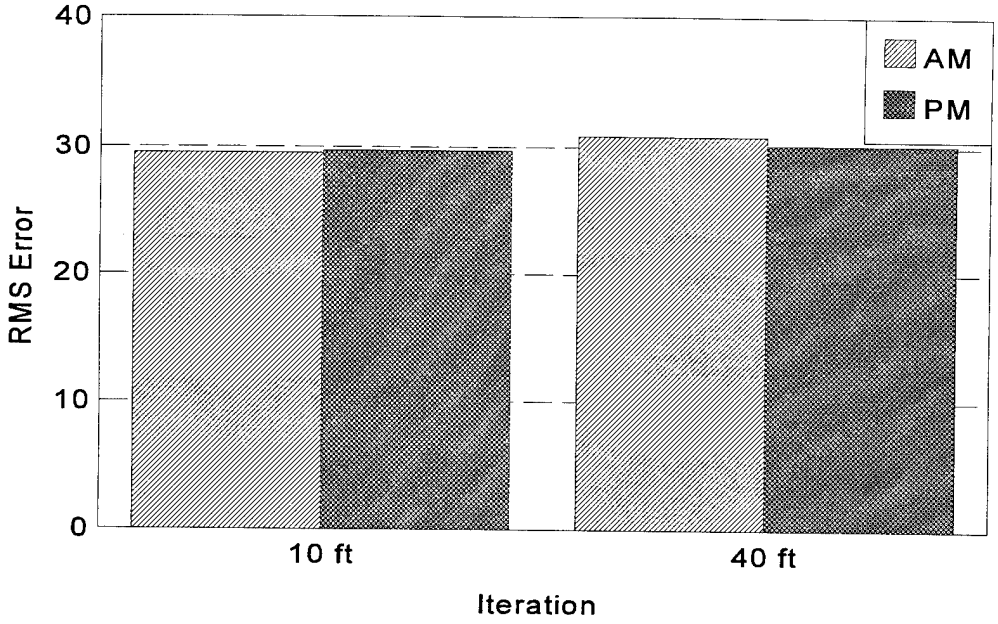

Figure 8. Interaction effects between session and iteration for altitude control during the straight hovers.

The ANOVA conducted for the interrupted night of sleep indicated a two-way interaction between session and iteration for altitude control ($F(1,9)=6.20$, $p=.0344$). Further analyses revealed that performance on the 10-foot hover was better than performance on the 40-foot hover during the afternoon session ($p<.05$), but the two hovers did not significantly differ during the morning session (0030).

A main effect for session occurred for heading control ($F(1,9)=9.66$, $p=.0126$) in which performance during the morning session (0030) was worse than the performance during the afternoon session. A main effect for iteration on altitude control ($F(1,9)=7.06$, $p=.0262$) indicated that performance on the 10-foot hover was better than performance on the 40-foot hover, as was the case on the full sleep nights.

Hovering turns

Two ANOVAs were conducted to determine the ability of subjects to maintain control of altitude during 10-foot and 40-foot hovering turns. The analysis for the full night of sleep revealed a three-way interaction among drug day, session, and

iteration (F(1,9)=56.25, p<.0001). Follow-up analyses indicated that performance on the 10-foot hover during the morning session (0600) following triazolam was worse than performance during the afternoon session (p<.05), with no effects occurring on the 40-foot hover. However, performance on the 40-foot hover during the morning session (0600) following placebo was worse than performance during the afternoon session following placebo (p<.05), but no effects were seen on the 10-foot hover. When comparing the two drugs, performance following triazolam was worse than performance following placebo during the afternoon session for the 40-foot hovering turn, but better than placebo on the 10-foot hovering turn (p<.05). There were no differences in performance during the morning session. These effects are depicted in Figure 9.

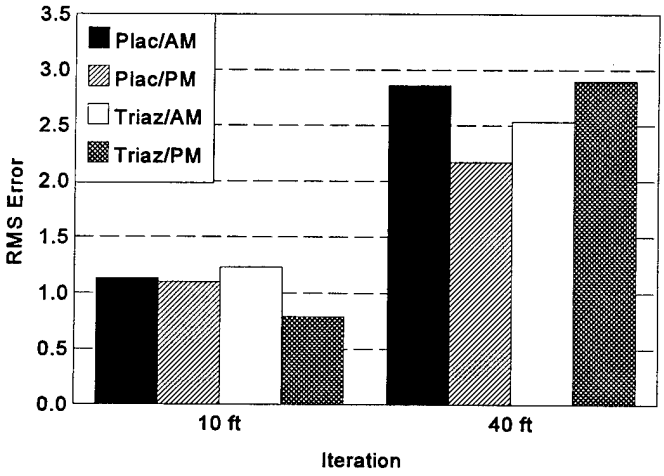

Figure 9. Interaction among drug day, session, and iteration for altitude control during the hovering turns.

A main effect occurred for session (F(1,9)=6.54, p=.0309), with the morning session (0600) showing worse performance than the afternoon session. A main effect for iteration also occurred (F(1,9)=60.17, p<.0001) because performance during the 40-foot hovering turn was worse than performance during the 10-foot hovering turn.

The ANOVA of the interrupted night of sleep revealed only a main effect for iteration (F(1,9)=58.71, p<.0001). Performance during the 40-foot hovering turn was worse than performance

during the 10-foot hovering turn. No other effects were observed.

Low-level navigation

Two ANOVAs were used to determine the ability of subjects to maintain control of heading, altitude, slip, and roll while using the GPS to navigate a low-level course. This part of the flight required the aviator to fly to six checkpoints, resulting in the scoring of four legs of the course.

The analysis of the full night of sleep indicated a two-way interaction between drug day and iteration for roll ($F(3,27)=3.74$, $p=.0227$). Further analyses indicated a statistically significant difference among the iterations during both the triazolam and placebo days. Contrasts indicated that performance during the first leg was significantly worse than performance during the second leg under both drug conditions, but performance on the first leg was worse than the fourth leg only during the placebo day, and not during the triazolam day ($p<.05$). Performance during the third leg of the navigation portion of the flight was worse than performance during the second and fourth legs under both drug conditions, but performance on the third leg also was worse than the first leg on the triazolam day, but not the placebo day ($p<.05$). The second leg also was worse than the fourth leg during the triazolam day but not during the placebo day ($p<.05$). Figure 10 indicates the performance for each leg of flight for each drug condition.

A significant main effect for session occurred on altitude control ($F(1,9)=12.81$, $p=.0059$). Performance during the morning session (0600) was significantly worse than performance during the afternoon session, regardless of the drug condition.

A significant main effect for iteration occurred on heading ($F(3,27)=27.34$, $p<.0001$), slip ($F(3,27)=7.96$, $p=.0006$), and roll ($F(3,27)=38.24$, $p<.0001$). For heading control, performance on the first and third legs of the course was worse than performance on the second and fourth legs ($p<.05$). For slip, performance on the first and third legs was again worse than performance on the second leg, and performance on the third leg was worse than performance on the fourth leg of the course ($p<.05$). For roll, performance on the first and third legs again was worse than

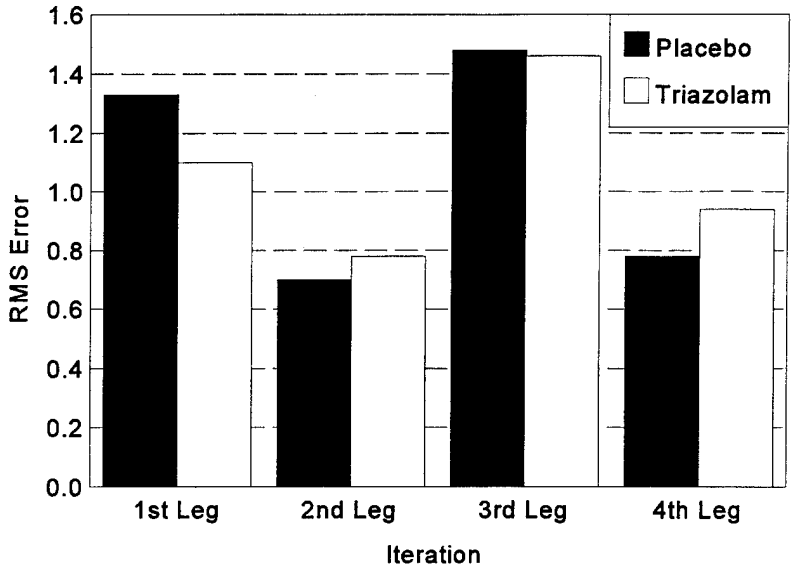

Figure 10. Interaction between drug day and iteration for roll during low-level navigation.

performance on the second and fourth legs of the course, but the first leg was better than the third leg ($p<.05$). Performance on the fourth leg of the course was worse than performance on the second leg of the course as well ($p<.05$). These effects are depicted in Figure 11.

In summary, after the full night of sleep, the best performance occurred during the second leg of the navigation portion, the longest portion of the flight (5 minutes). The poorest performance occurred during the third leg, one of the two shortest legs (2 minutes).

The ANOVA for the interrupted night of sleep indicated a three-way interaction among drug day, session, and iteration for roll ($F(3,27)=5.60$, $p=.0040$). Follow-up analyses indicated that on the first leg of the flight during the placebo day, performance was better during the afternoon session than during the morning session at 0030 ($p<.05$). This effect was not present during the triazolam day.

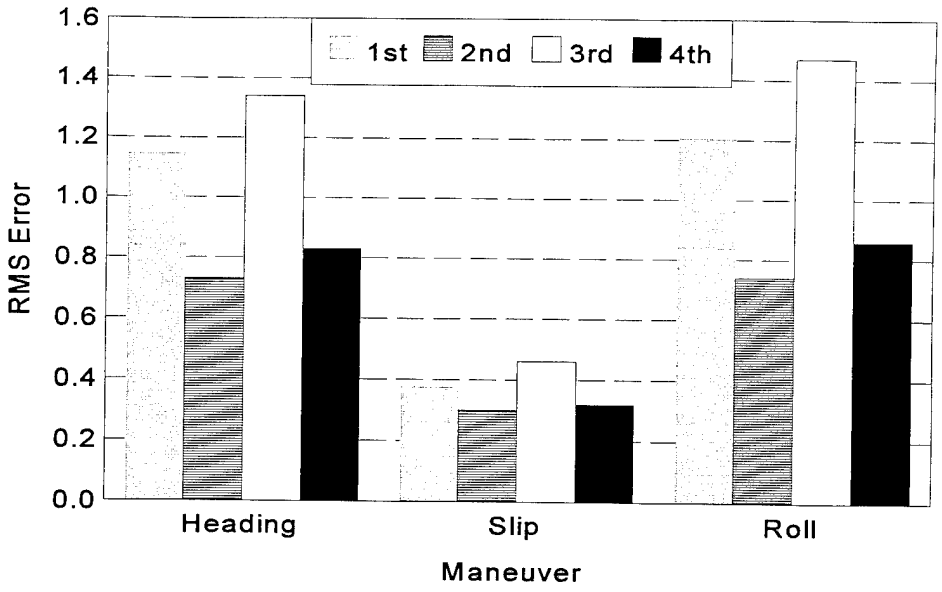

Figure 11. Main effect for iteration for heading control, slip, and roll during low-level navigation.

A main effect for drug day occurred for altitude ($F(1,9)=6.75$, $p=.0289$). Overall performance during the triazolam day was worse than that during the placebo day. A main effect for session also occurred for heading ($F(1,9)=10.68$, $p=.0097$), altitude ($F(1,9)=28.99$, $p=.0004$), and roll ($F(1,9)=5.20$, $p=.0485$). Inspection of the means for each of these measures indicated that performance was significantly worse during the morning session (0030) than during the afternoon session ($p<.05$), regardless of the drug condition.

A main effect for iteration occurred on heading ($F(3,27)=12.52$, $p<.0001$), slip ($F(3,27)=12.52$, $p<.0001$), and roll ($F(3,27)=20.78$, $p=.0073$). For heading and roll, performance during the first leg of the navigation portion of the flight was worse than performance on the second and fourth legs ($p<.05$). Performance on the second leg was better than performance on the third and fourth legs, and performance on the fourth leg was better than performance on the third leg ($p<.05$). For slip, performance on the first, second, and fourth legs were significantly better than performance on the third leg ($p<.05$). These effects are depicted in Figure 12.

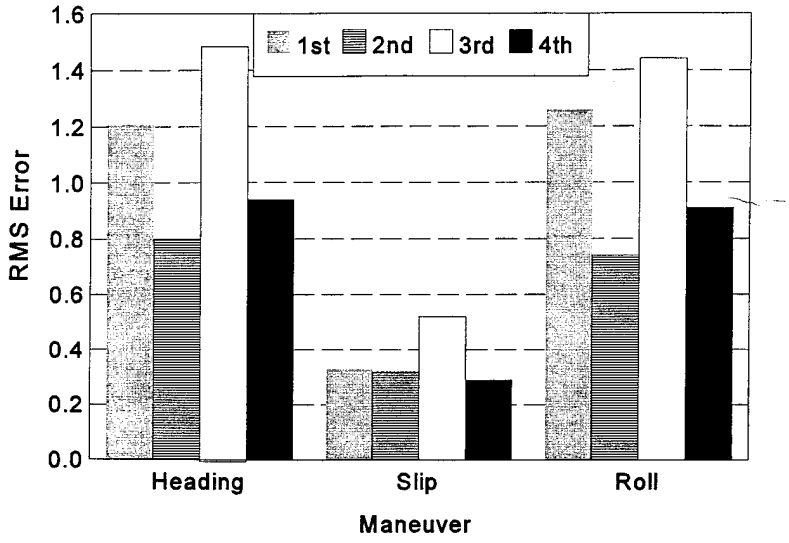

Figure 12. Main effect for iteration for heading control, slip, and roll during low-level navigation.

In summary, the iteration main effect indicated that performance on the low-level navigation portion of the flight during the interrupted night of sleep was best on the second leg of the flight, the longest leg of the course (5 minutes), and performance was worse on the third leg of the course, one of the two shortest legs of the course (2 minutes). These effects are similar to the effects found during the full night of sleep.

Straight-and-levels

The four straight-and-level maneuvers were analyzed in terms of the subject's ability to maintain control of heading, altitude, airspeed, and roll. The first three maneuvers were performed with the AFCS engaged, and the fourth maneuver was performed with the AFCS off. The ANOVA for the full night of sleep for this maneuver indicated a three-way interaction among drug day, session, and iteration for control of roll ($F(3,27)=2.94$, $p=.0510$). Post hoc analyses revealed that roll control on the first straight-and-level was better than the second, third, and fourth straight-and-levels during the morning session (0600) following triazolam ($p<.05$) but not placebo. This effect also was present during the afternoon session following triazolam, but not following placebo. In addition, the second straight-and-level was worse than the third straight-and-level

and better than the fourth on the placebo day in the morning. Also, performance during the morning session on the first straight-and-level on the triazolam day was better than the afternoon session, but performance on the third straight-and-level was worse during the morning session following triazolam than during the afternoon session ($p<.05$). (See Figure 13)

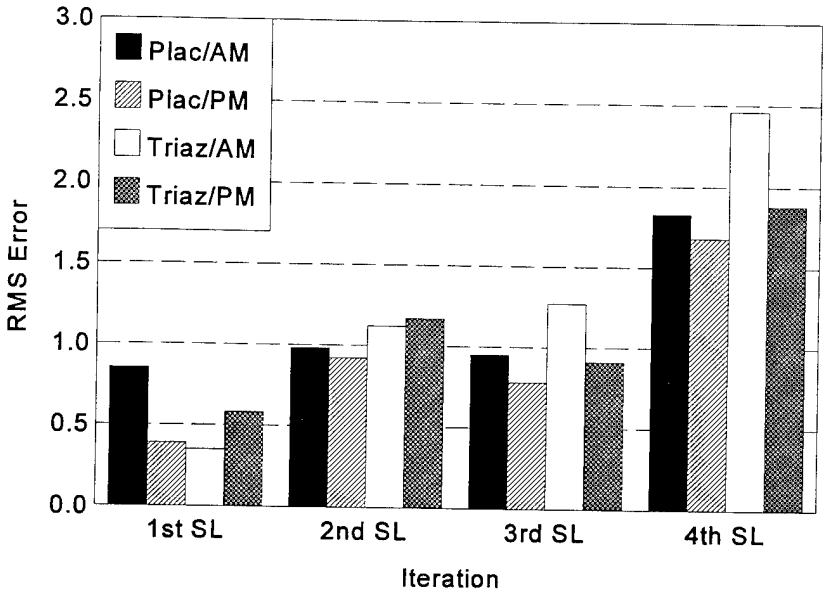

Figure 13. Interaction among drug day, session, and iteration for control of roll.

The analyses also revealed a two-way interaction between drug day and iteration on airspeed ($F(3,27)=3.00$, $p=.0479$). This was attributable to performance being worse on the second straight-and-level maneuver following triazolam than performance following placebo ($p<.05$), while there were no drug-related differences on the other straight-and-levels. These effects are indicated in Figure 14.

A main effect for drug day was found on roll control ($F(1,9)=9.85$, $p=.0120$), with performance following triazolam worse than performance following placebo. A main effect for session was indicated for control of altitude ($F(1,9)=18.34$, $p=.0020$), airspeed ($F(1,9)=17.37$, $p=.0024$), and roll ($F(1,9)=7.74$, $p=.0214$). In all measures, performance during the morning session (0600) was worse than performance during the afternoon session ($p<.05$).

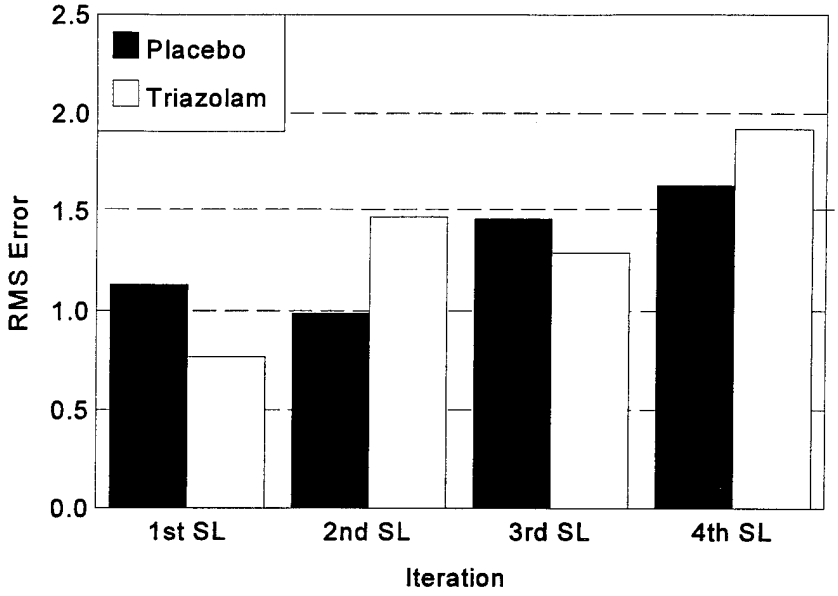

Figure 14. Interaction between drug day and iteration for airspeed during low-level navigation.

A main effect for iteration also occurred on control of heading ($F(3,27)=13.07$, $p<.0001$), altitude ($F(3,27)=11.32$, $p=.0001$), airspeed ($F(3,27)=11.88$, $p<.0001$), and roll ($F(3,27)=45.47$, $p<.0001$). Post hoc comparisons indicated performance on the first straight-and-level was better than performance on the second, third, and fourth straight-and-level for every measure ($p<.05$). In addition, performance the third straight-and-level was better than the second straight-and-level on heading control ($p<.05$). Performance on the second straight-and-level was better than performance on the fourth straight-and-level for measures of altitude, airspeed, and roll ($p<.05$), and performance on the third straight-and-level was better than performance on the fourth straight-and-level for measures of heading, airspeed, and roll ($p<.05$). These effects are shown in Figure 15.

The ANOVA for the interrupted night of sleep indicated a two-way interaction between drug day and iteration on control of heading ($F(3,27)=3.99$, $p=.0179$). Further analyses indicated that performance on the first straight-and-level was better than performance on the second, third and fourth straight-and-levels,

and performance on the third straight-and-level was better than performance on the second following both triazolam and placebo. Performance on the third straight-and-level was better than performance on the fourth following triazolam ($p<.05$), but not following placebo. These effects are illustrated in Figure 16.

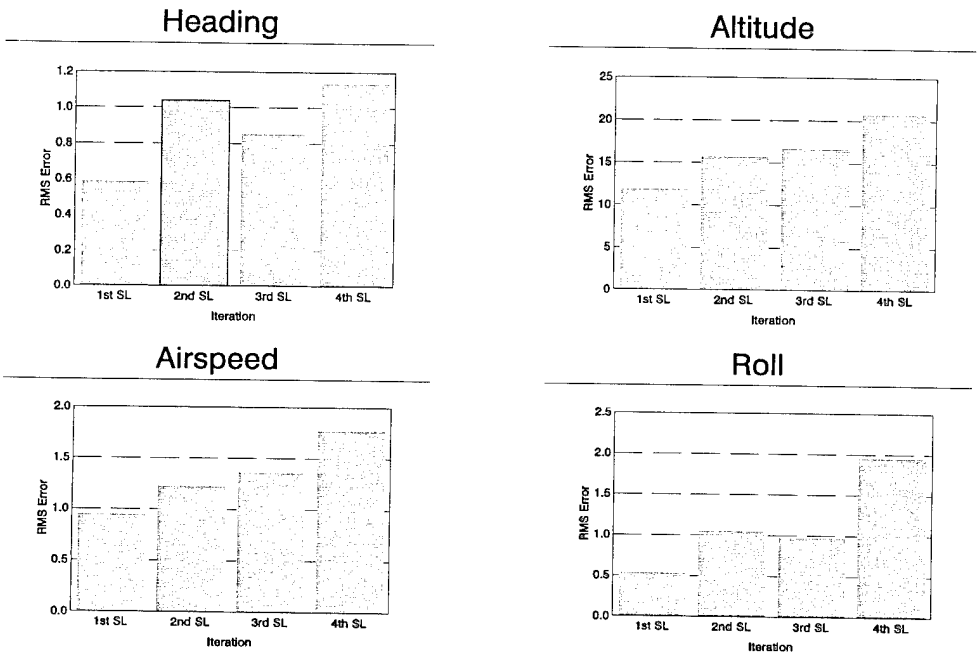

Figure 15. Main effect for iteration for heading, altitude, airspeed, and roll.

A main effect for session occurred on heading ($F(1,9)=21.22$, $p=.0013$), altitude ($F(1,9)=5.96$, $p=.0373$), and roll ($F(1,9)=18.50$). For each of these measures, performance during the morning session (0030) was worse than performance during the afternoon session. A main effect for iteration also occurred on heading ($F(3,27)=22.50$, $p<.0001$), altitude ($F(3,27)=24.01$, $p<.0001$), airspeed ($F(3,27)=16.04$, $p<.0001$), and roll ($F(3,27)=36.92$, $p=.0001$). Post hoc comparisons indicated performance on the first straight-and-level was better than

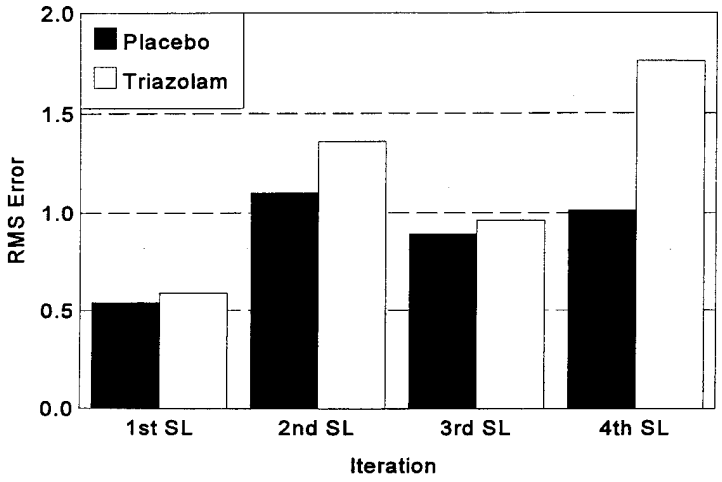

Figure 16. Interaction between drug day and iteration for control of heading during low-level navigation.

performance on the second, third, and fourth for every measure ($p<.05$). Performance on heading and roll control was better during the third straight-and-level than during the second ($p<.05$). Performance on altitude, airspeed, and roll during the second straight-and-level was better than during the fourth ($p<.05$), and performance on during the third straight-and-level was better on all the measures than during the fourth straight-and-level ($p<.05$). These effects are shown in Figure 17.

Left standard-rate turns

The two left standard-rate turns were analyzed with two repeated measures ANOVAs (one for the full night and one for the interrupted night of sleep) to determine the ability of subjects to maintain control of turn rate, altitude, airspeed, slip, and roll. The first turn was conducted with the AFCS engaged, while the second turn was conducted with the AFCS turned off. The analysis of the full night of sleep indicated a three-way interaction among drug day, session, and iteration for control of altitude ($F(1,9)=14.24$, $p=.0044$). Comparison of the two drug conditions indicated that performance following triazolam was worse than placebo on the first turn during the morning session (0600), and worse than placebo on the second turn during the afternoon session ($p<.05$). These effects are illustrated in Figure 18.

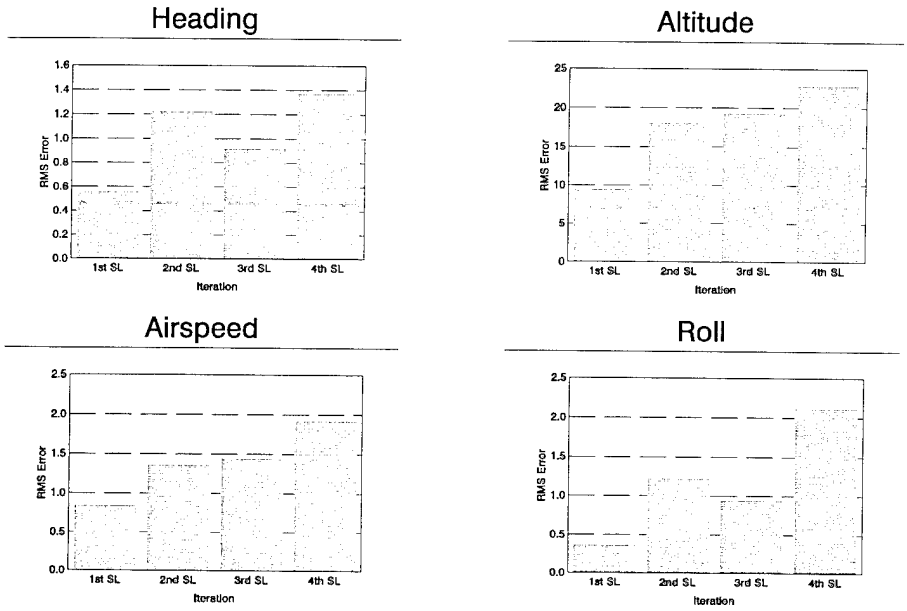

Figure 17. Main effect for iteration for heading, altitude, airspeed, and roll during low-level navigation.

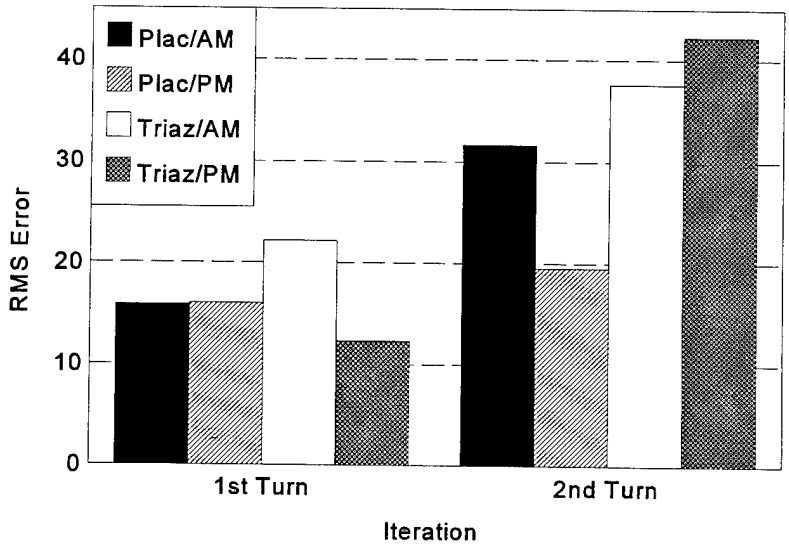

Figure 18. Interaction among drug day, session, and iteration for control of altitude.

There was a significant two-way interaction between drug day and iteration for altitude ($F(1,9)=5.02$, $p=.0518$) and airspeed ($F(1,9)=6.53$, $p=.0309$). Post hoc analyses indicated that performance on both measures was worse on the second turn than on the first turn following both triazolam and placebo; however, the difference between the two iterations was greater following triazolam than following placebo, as can be seen in Figure 19.

A main effect occurred for drug day on turn rate ($F(1,9)=5.70$, $p=.0408$) because performance following triazolam was worse than performance following placebo. Another main effect was indicated for session on airspeed ($F(1,9)=13.36$, $p=.0053$). This was due to poorer performance during the morning (0600) than during the afternoon. A final main effect occurred for iteration on turn rate ($F(1,9)=9.58$, $p=.0128$), altitude ($F(1,9)=23.45$, $p=.0009$), airspeed ($F(1,9)=22.90$, $p=.0010$), slip ($F(1,9)=19.26$, $p=.0017$), and roll ($F(1,9)=50.32$, $p=.0001$). Performance for each of these measures was worse during the second turn than the first turn ($p<.05$).

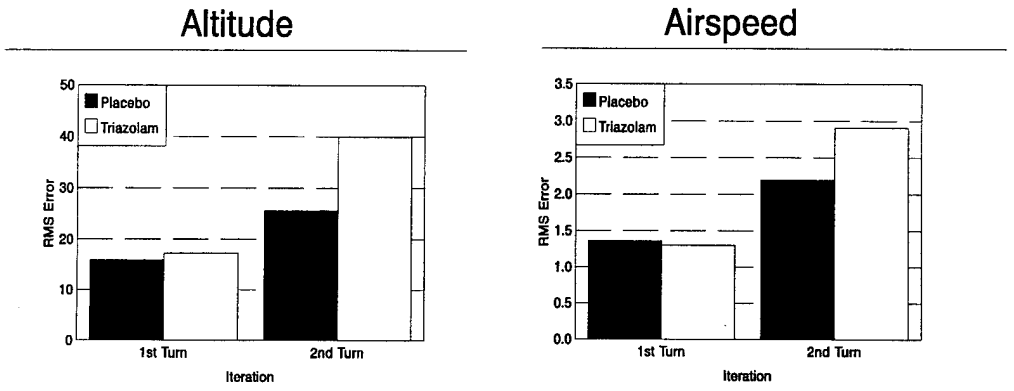

Figure 19. Interaction between drug day and iteration for altitude and airspeed control during the left standard rate turn.

The ANOVA for the interrupted night of sleep revealed two different two-way interactions. The first interaction occurred between drug day and session on slip control ($F(1,9)=6.45$, $p=.0317$). Post-hoc analyses indicated that performance was worse during the morning session (0030) than during the afternoon session under triazolam ($p<.05$), but no differences occurred under placebo. These effects are illustrated in Figure 20.

The second two-way interaction occurred between session and iteration on slip ($F(1,9)=6.21$, $p=.0343$). Post-hoc analyses indicated that performance was worse on the second turn than on the first turn during both the morning and afternoon sessions ($p<.05$), but the difference between the two turns was more pronounced during the morning session than during the afternoon session.

A main effect occurred for session on turn rate ($F(1,9)=19.73$, $p=.0016$), altitude ($F(1,9)=11.74$, $p=.0075$), airspeed ($F(1,9)=11.99$, $p=.0071$), and roll ($F(1,9)=16.41$, $p=.0029$). For each of these measures, performance during the morning (0030) was significantly worse than performance during the afternoon. Another main effect occurred for iteration on turn rate ($F(1,9)=14.47$, $p=.0042$), altitude ($F(1,9)=26.04$, $p=.0006$), airspeed ($F(1,9)=18.98$, $p=.0018$), slip ($F(1,9)=22.41$, $p=.0011$), and roll ($F(1,9)=51.76$, $p=.0001$). For each of these measures, performance was worse on the second turn than on the first turn.

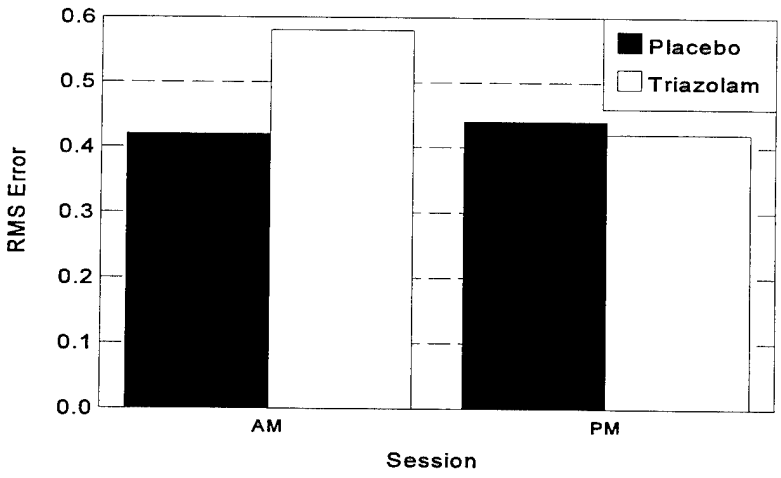

Figure 20. Interaction between drug day and session for slip during the left standard rate turn.

Straight climbs

Two three-way ANOVAs (drug day x session x iteration) were conducted to determine the ability of the pilot to perform a straight climb while controlling heading, airspeed, slip, roll,

and rate-of-climb. The climb maneuver occurred twice during the flight profile, both with the AFCS engaged.

The ANOVA for the full night of sleep revealed a main effect for drug day on airspeed ($F(1,9)=5.25$, $p=.0476$) and rate of climb ($F(1,9)=5.75$, $p=.0400$). The performance during the triazolam day was worse than the performance during the placebo day for both parameters. There was a tendency for a similar effect on slip, although this did not reach statistical significance ($p=.07$).

A main effect for session occurred on heading ($F(1,9)=6.11$, $p=.0355$) and roll ($F(1,9)=4.97$, $p=.0528$), with the morning session (0600) showing worse performance than the afternoon session. A main effect for iteration occurred on airspeed ($F(1,9)=35.75$, $p=.0002$), slip ($F(1,9)=6.11$, $p=.0354$), and roll ($F(1,9)=6.00$, $p=.0368$). Each of these measures indicated poorer performance during the first climb than during the second ($p<.05$). This may have been because the second climb was for 120 seconds while the first climb was for only 60 seconds.

The ANOVA for the interrupted night of sleep revealed a main effect for iteration on airspeed ($F(1,9)=6.93$, $p=.0272$) and slip ($F(1,9)=23.67$, $p=.0009$). Inspection of the means indicated the effect was the same as the one which occurred after the full night of sleep; performance during the second climb was worse than during the first ($p<.05$). No main effects for drug day or session occurred.

Right standard-rate turns

Two ANOVAs were used to analyze the three right standard-rate turns to determine the ability of subjects to maintain control of turn rate, altitude, airspeed, slip, and roll. The first and second turns were conducted with the AFCS engaged, while the third turn was conducted with the AFCS turned off.

The analysis of the full night of sleep indicated a three-way interaction among drug day, session, and iteration for the roll measure ($F(2,18)=3.62$, $p=.0477$). Further analyses revealed that performance on the third turn during the morning (0600) under triazolam was worse than performance under placebo ($p<.05$), but this effect did not occur during the afternoon session. These effects are shown in Figure 21.

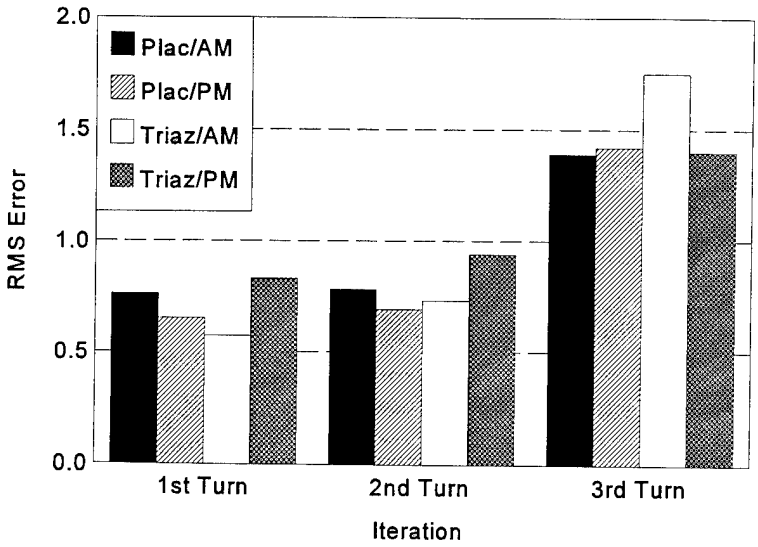

Figure 21. Interaction among drug day, session, and iteration for roll during the right standard rate turn.

A main effect for iteration occurred for turn rate ($F(2,18)=39.04$, $p<.0001$), altitude ($F(2,18)=21.42$, $p<.0001$), slip ($F(2,18)=10.39$, $p=.0010$), and roll ($F(2,18)=16.03$, $p=.0001$). For slip, performance on the second turn was significantly better than performance on the first and third turns ($p<.05$). For the other measures (turn rate, altitude, and roll), performance on the first and second turns was significantly better than performance on the third ($p<.05$). There was no significant difference between performance on the first and second turns.

The ANOVA for the interrupted night of sleep indicated a three-way interaction among drug day, session, and iteration for slip ($F(2,18)=6.25$, $p=.0087$). Performance on the first turn for the triazolam day was better during the morning session than during the afternoon session, but the morning session performance was worse than the afternoon session performance for the placebo day. These differences did not occur under either drug for the second and third turns. Figure 22 shows these effects.

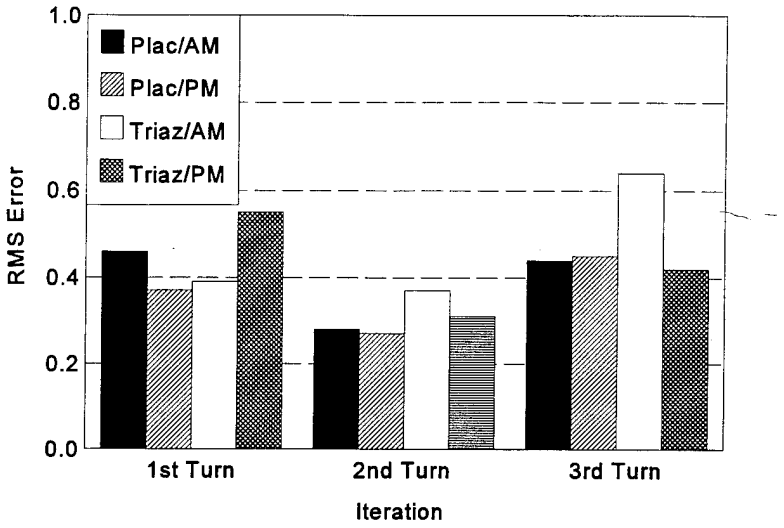

Figure 22. Interaction among drug day, session, and iteration for slip during the right standard rate turn.

Two separate two-way interactions were revealed. The first one occurred between drug day and session on turn rate ($F(1,9)=6.85$, $p=.0280$), altitude ($F(1,9)=7.34$, $p=.0240$), and airspeed ($F(1,9)=9.27$, $p=.0139$). All three measures showed worse performance on the triazolam day when compared to the placebo day during the morning session ($p<.05$), but not during the afternoon session. In addition, on the triazolam day, performance on airspeed was worse during the morning (0030) session than during the afternoon session. These effects are shown in Figure 23.

The second two-way interaction occurred between drug day and iteration for altitude ($F(2,18)=5.96$, $p=.0385$). Further analyses indicated that performance on the second turn during the placebo day was worse than performance on the first and third turn ($p<.05$), but there were no differences among the turns during the triazolam day.

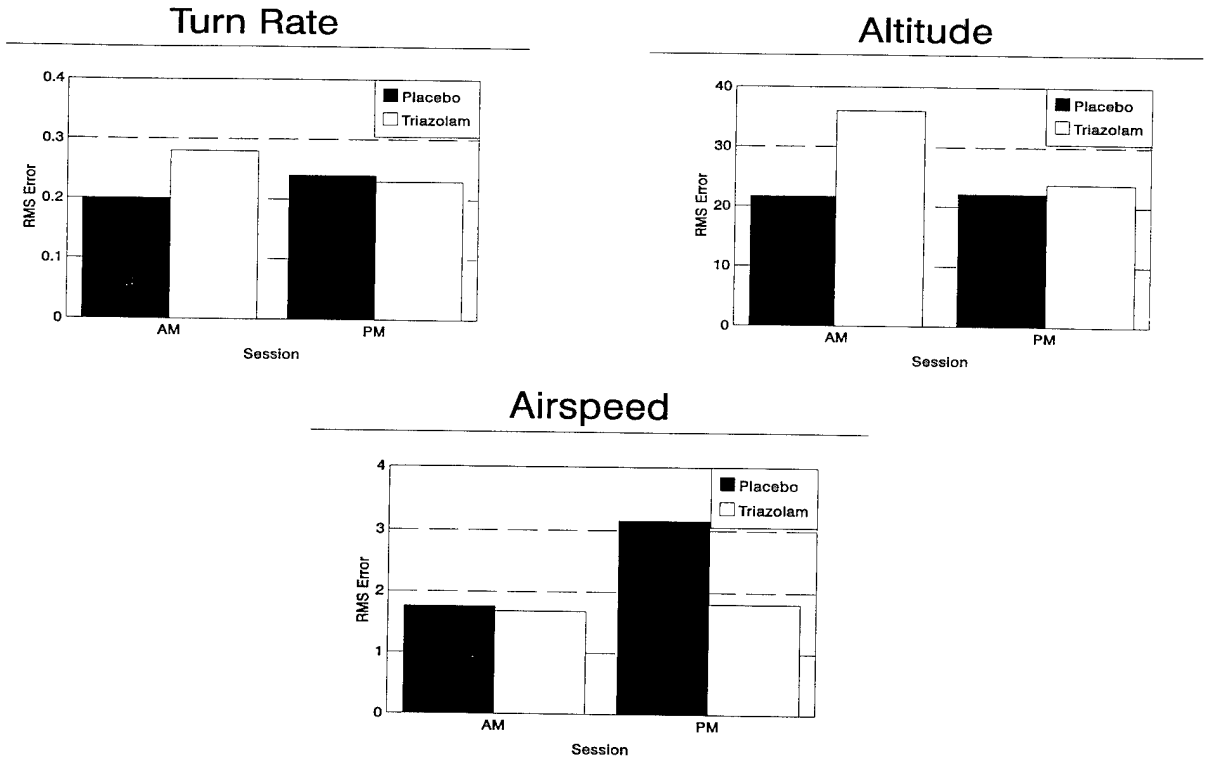

Figure 23. Interaction between drug day and session for turn rate, altitude, and airspeed during the right standard rate turn on the interruption night.

A main effect for drug day occurred on altitude ($F(1,9)=7.25$, $p=.0247$) and airspeed ($F(1,9)=5.71$, $p=.0406$). On both measures, performance during the triazolam day was worse than performance during the placebo day ($p<.05$). Another main effect occurred for session on airspeed ($F(1,9)=5.76$, $p=.0398$) and roll ($F(1,9)=5.17$, $p=.0490$). On both measures, performance was worse during the morning session (0600) than during the afternoon session, regardless of drug condition. A final main effect occurred for iteration on turn rate ($F(2,18)=39.09$, $p<.0001$), altitude ($F(2,18)=4.59$, $p=.0245$), airspeed ($F(2,18)=6.82$, $p=.0063$), slip ($F(2,18)=8.14$, $p=.0030$), and roll ($F(2,18)=36.83$, $p<.0001$). On turn rate, altitude, airspeed, and slip, performance on the second turn was better than performance on the third turn ($p<.05$). In addition, on slip, performance on the second turn was better than performance on the first turn ($p<.05$). For turn rate and roll, performance on the third turn was worse than performance on the first and second turns ($p<.05$).

Straight descents

Two three-way ANOVAs (drug day x session x iteration) were conducted to determine the ability of the pilot to perform a straight descent while controlling heading, airspeed, slip, roll, and rate of descent. The profile incorporated three straight descents, all with the AFCS turned off.

The ANOVA for the full night of sleep revealed a drug day main effect on heading ($F(1,9)=5.20$, $p=.0485$) and roll ($F(1,9)=6.99$, $p=.0268$), with performance after triazolam worse than performance after placebo. A main effect for session also occurred on roll ($F(1,9)=6.84$, $p=.0280$) and rate of descent ($F(1,9)=7.82$, $p=.0209$). Both of these measures indicated poorer performance during the morning session (0600) than during the afternoon session.

The ANOVA for the interrupted night of sleep revealed a three-way interaction among drug day, session, and iteration ($F(1,9)=3.71$, $p=.0448$); however, follow-up analyses did not reveal any significant differences among the means. A main effect for session occurred for rate of descent ($F(1,9)=6.28$, $p=.0335$). Inspection of the means indicated poorer performance during the morning flight (0030) than during the afternoon flight.

Left descending turn

Two ANOVAs were conducted to determine the ability of subjects to maintain control of turn rate, airspeed, slip, roll, and rate of descent during a left descending turn. This maneuver was performed with the AFCS turned off. The analyses of both the full night of sleep and the interrupted night showed no significant effects for any of the measures.

Discussion

Sleepiness scale

No drug effects were statistically significant for subjective sleepiness. However, there was a great deal of variability among the subjects' responses. There was a tendency for more sleepiness 20 minutes after awakening than during the remainder of the day, regardless of drug condition, and subjective sleepiness was also higher 15 minutes before bedtime

as compared to the late morning and afternoon ratings. The lack of statistically significant subjective indications of sleepiness may have been due to the unwillingness of aviators to express sleepiness during a time when they were about to perform their assigned tasks.

Performance Assessment Battery

There were no differences between drug conditions in cognitive performance on this battery of tests. The MAST-6, a scanning and memory test, did show that morning performance was slower than afternoon performance, as did the logical reasoning test; however, this effect was not influenced by whether the subjects were under placebo or triazolam. The slower morning performance was probably attributable to the fact that subjects were somewhat sleepy at this time since the morning session occurred approximately 3.5 hours after rising from sleep.

Electroencephalography assessments

Several drug effects were evident in the resting EEG which were conducted to determine the physiological state of the subjects following placebo and triazolam. More of the slower frequencies (alpha, theta, and delta bands) occurred following the placebo night than following the triazolam night. Slow activity is associated with relaxation or sedation, which one would expect if the effects of triazolam had been evident during the day. Since more slow activity occurred after the placebo night than after the triazolam night, it would appear that the effects of the active hypnotic had dissipated by the time of the first EEG session, about 12 hours postdose. The slower activity which occurred after the placebo night may have been due to the subjects' having less restful sleep during the placebo night than during the triazolam night. Even though there was more slow wave sleep on the placebo nights than on the triazolam nights, the sleep during the placebo night showed more light sleep (stage 1) and more awake time than during the triazolam night, leading to lower daytime physiological alertness after placebo than after triazolam.

Polysomnographic analysis

Sleep architechture following administration of triazolam was affected by the drug. There was more slow wave sleep after placebo than after triazolam, an effect inconsistent with some of

the previous literature which indicates that triazolam has no effect on slow wave sleep. However, there was more stage 2 sleep following triazolam than following placebo which has been shown in other studies. In addition, there was less stage 1 and awake time after sleep onset following triazolam than following placebo. This would indicate that sleep with triazolam was more restful than sleep with placebo. On the sleep interrupt night, triazolam was especially helpful in returning to sleep after the 0030 flight. The sleep latency on the placebo nights tended to be long, giving a shorter total amount of sleep for that night. Even though the subjects in this experiment were not complaining of sleep problems, it is reasonable that sleep would be more restful after triazolam than after placebo since sleep under laboratory conditions may be more disrupted due to the unfamiliar surroundings than one's normal sleep would be (Dement, Kahn, and Roffwarg, 1965; Agnew, Webb, and Williams, 1966).

It may be operationally significant that the amount of time for the subjects to awaken to the morning wake-up signal tended to be longer following triazolam than following placebo. Although this effect was not statistically significant due to the high variability among the subjects, it is a point of concern when prescribing triazolam to personnel. Individual reactions to a sleeping aide should be assessed before a soldier is given a hypnotic and then be required to awaken in the morning with only the usual wake-up cue. Those individuals who are sensitive to the effects of hypnotics should be apprised of the possibility of a slow wake-up the next morning.

Of greater concern is the fact that some subjects responded very slowly to the midnight wake-up call after triazolam compared to placebo. It was expected that most people would react slowly to the early wake-up call since the drug should be near its peak approximately 2 hours post-administration. Most of the subjects awakened within a few seconds of the wakeup call, but the few who were slow, and the one who needed to be awakened by the technician, are of concern. The aviation community was particularly interested in the ability of aviators to respond to an emergency after being administered a hypnotic. It is the individual sleep inertia tendencies caused by an hypnotic that makes test doses valuable. If one is aware of how the drug affects him specifically, measures can be taken to compensate for these effects.

While waking up early after triazolam administration presented a problem for some subjects, returning to sleep after flying their mission was much faster during the triazolam night than during the placebo night. Of the 10 subjects tested, 8 were asleep in less than 10 minutes during the triazolam night, while 6 were still awake after 30 minutes during the placebo night. This can be considered a positive effect of triazolam because it may be difficult for aviators to sleep in the field, which will lead to degradation of performance. The ability to return to sleep after an interruption is important. Triazolam was helpful in this respect and may be the reason the sedation was apparent in the EEG measures during the day following placebo. The sleep measures indicated more awake time and more stage 1 sleep during the placebo night than during the triazolam night which would indicate that many aviators became partially sleep deprived on the placebo interruption night.

Flight performance

The major question for this study was whether aviators can fly their mission after a drug-induced sleep. Analysis of the data indicated that performance following triazolam is affected adversely. Even though aviators were still able to fly the profile with few obvious decrements under triazolam, subtle differences in performance were evident for most of the maneuvers measured. Of the nine maneuvers flown, five had significant decreases in performance following a full night of sleep with triazolam when compared to performance after a full night of sleep with placebo, regardless of the session. However, in some cases, the drug effect was evident during the 0600 session (8 hours postdose), but not the 1300 session (15 hours postdose), with the performance after the triazolam night worse than the performance after the placebo night. This effect occurred in three maneuvers - the hovering turn, the left standard rate turn, and the right standard rate turn.

The flight which occurred at 0030, 2 hours postdose, showed significant performance decrements on some of the maneuvers. Two of the maneuvers indicated a drug effect during this early morning flight. On both the left and right standard rate turns, performance during the 0030 session on the triazolam night was worse than performance on the placebo night. No other drug-related effects were significant during this flight. However, there were overall session effects, regardless of the drug condition, on six of the maneuvers, with performance during the

0030 session being worse than performance during the 1300 session. The reason for the lack of statistically significant drug effects may again be due to individual reactions to the drug which led to high variability in the data.

Side effects of drug-administration

No physiological effects such as daytime sleepiness and anxiety were reported by any of the subjects in the study. A measure of amnesia was taken each morning of the study, and two of the subjects indicated they had no recall of the details of the mission flown at 0030 following triazolam administration. Although they remembered having flown the simulator, they were not able to recall some of the portions of the 2 hours they were awake and performing tasks. This side effect is a concern for the aviation community since it is important that aviators remember the details of the missions they fly and be able to report back to the unit what occurred during the flight. This side effect does not occur with every person who consumes triazolam; however, it does occur with some people, and occurs most frequently when the person is awakened early after administration of triazolam. This is another reason why a test dose of the drug is imperative. It is important to know what each individual's response to the drug will be in order to compensate for these potential responses.

Conclusions

The purpose of this investigation was two-fold: to determine if an aviator can fly his mission after 8 hours of sleep with triazolam, and whether an aviator can be awakened shortly after administration of triazolam and fly his mission. Both of these questions were addressed in the study. The findings indicate that flight performance generally is affected by triazolam, particularly in the morning, but this effect usually dissipates by the afternoon. However, the decrements in performance are not so large that the aviator is in eminent danger of crashing the aircraft. Of concern is the fact that these subtle changes were seen in the performance of maneuvers that are well-practiced, and they may be more severe in situations where the aviator is confronted with unusual demands such as those which occur during an emergency. This is an area which needs further investigation before definite conclusions can be drawn.

Polysomnographic measures indicate that triazolam leads to more restful sleep even in those not complaining of sleep problems, and this effect will help to promote alertness when an aviator is left to sleep in unusual, uncomfortable environments. This effect was shown in the resting EEG; the day after placebo showed more slow activity than the day after triazolam, indicating that aviators were less alert after sleeping in an unusual environment. Although the sleep with triazolam had less slow wave sleep than that with placebo, triazolam helped aviators sleep with few awakenings, and return to sleep quickly after they were awakened in the middle of the night.

Two major concerns beyond the flight performance effects are the slowness of a few subjects to wake to a call after only 2 hours postadministration (one needed a physical prompt to awaken), and the amnesia of mission details seen in two subjects. Although these behaviors occurred in only a small portion of the subjects in this study, it is a concern which should be addressed before an aviator is administered hypnotics. Both these effects emphasize the importance of the test dose of the medication before an aviator is prescribed a hypnotic when an important mission could occur.

In conclusion, performance is affected somewhat by triazolam administered 8 hours before a flight, although it has almost no effects when administered 2 hours before a flight when compared to placebo. The aviator is capable of flying the mission; however, it is not known how the slight decrements observed in well-practiced maneuvers may predict performance which occurs if something unusual should arise during the flight. It is also important to administer the hypnotic to the aviator first under controlled conditions, including a wake-up shortly following administration, to test for unusual effects from the drug such as amnesia or unusually long responses to a wake-up call. Further research is needed to determine responses to emergency situations.

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List of manufacturers

BMDP Statistical Software, Inc.
1440 Sepulveda Blvd.
Los Angeles, CA 90025

Cadwell Laboratories
909 North Kellogg Street
Kennewick, WA 99336

Grass Instruments, Incorporated
Box 2551
Lehigh Valley, PA 18001

Digital Equipment Corporation
P.O. Box C52008
Nashua, NH 03061-2008

Perkin Elmer Corporation
Marn Avenue
Norwalk, CT 06886

Zenith Data Systems
1945 Old Gallows Road
Suite #204
Vienna, VA 22180

Appendix A

Informed Consent Agreement

VOLUNTEER AGREEMENT AFFIDAVIT

For use of this form, see AR 70-25 or AR 40-38; the proponent agency is OTSG.

PRIVACY ACT OF 1974

Authority: 10 USC 3101, and 10 USC 1071-1087

Principal Purpose: To document voluntary participation in the Clinical Investigation and Research Program. SSN and home address will be used for identification and locating purposes.

Routine Uses: The SSN and home address will be used for identification and locating purposes. Information derived from the study will be used to document the study; implementation of medical programs; adjudication of claims; and for the mandatory reporting of medical conditions as required by law. Information may be furnished to Federal, State, and local agencies.

Disclosure: The furnishing of your SSN and home address is mandatory and necessary to provide identification and to contact you if future information indicates that your health may be adversely affected. Failure to provide the information may preclude your voluntary participation in this investigational study.

PART A – VOLUNTEER AFFIDAVIT

Volunteer Subjects in Approved Department of the Army Research Studies

Volunteers under the provisions of AR 40-38 and AR 70-25 are authorized all necessary medical care for injury or disease which is the proximate result of their participation in such studies.

I, _____ SSN_____,

having full capacity to consent and having attained my _____ birthday, do hereby volunteer to

participate in the study entitled "Effects of triazolam on sleep inertia and pilot performance"

under the direction of J. Lynn Caldwell, Ph.D., Research Psychologist

conducted at USAARL, Fort Rucker, AL.

The implications of my voluntary participation; duration and purpose of the research study; the methods and means by which it is to be conducted; and the inconveniences and hazards that my reasonable by expected have been explained to me by Dr. Lynn Caldwell.

I have been given an opportunity to ask questions concerning this investigational study. Any such questions were answered to my full and complete satisfaction. Should any further questions arise concerning my rights or study-related injury, I may contact

Command Judge Advocate General Office

at HQ, USAMRDC, Fort Detrick, Frederick, MD AV 343-2065 Comm 301-663-2065

I understand that I may at any time during the course of the study revoke my consent and withdraw from the study without further penalty or loss of benefits; however I may be required (military volunteer) or requested (civilian volunteer) to undergo certain examinations if, in the opinion of the attending physician, such examinations are necessary for my health and well-being. My refusal to participate will involve no penalty to which I am otherwise entitled.

PART B -- TO BE COMPLETED BY INVESTIGATOR

INSTRUCTIONS FOR ELEMENTS OF INFORMED CONSENT: *(Provide a detailed explanation in accordance with Appendix C, AR 40-38 or AR 70-25.)*

SEE ATTACHED SHEETS.

I do ☐ do not ☐ *(check one & initial)* consent to the inclusion of this form in my outpatient medical treatment record.

SIGNATURE OF VOLUNTEER	DATE
PERMANENT ADDRESS OF VOLUNTEER	TYPED NAME OF WITNESS
	SIGNATURE OF WITNESS / DATE

You are being asked to participate in a study which will determine the ability of a person to fly an aircraft after administration of a sleeping aid, both the day following a full night's sleep and at night after being awakened during the sleep period. You will take either Halcion (triazolam, a benzodiazepine) or a placebo before bedtime and will sleep in a private bedroom in the laboratory. Your brain activity will be monitored while you sleep in order to determine the quality of sleep you receive each night. Each day you will fly the simulator for approximately 3 hours (1.5 hours in the morning and 1.5 hours in the afternoon), perform cognitive tasks to test your reaction time and performance, and have your brain activity recorded while you are both resting and performing tasks in order to assess the effects of the sleeping aids on next day performance.

You are to come to the laboratory the first day of the study. On this day, you will undergo a medical screen for possible sensitivities to benzodiazepines and any other medical condition which may be complicated by use of a benzodiazepine. This screening will be accomplished by a flight surgeon interview and review of your medical records. After the medical monitor has approved your participation in the study, you will begin training for the flight profile and the cognitive tests. Additionally, you will be administered a personality test which is used as descriptive information only. The results of this test is added to a data base which is being used to look at groups of aviators and their personalities. Your name will be removed from this inventory and the information will be used in group form only.

You will be housed at the laboratory for 10 nights (11 days), including the weekend, and you will be released at approximately 1700 on the last day of the study (Thursday). We will provide food and toilet articles for you at no expense. You may leave the laboratory on some of the days after you have completed testing for the day, however, most of the time you will be required to stay in the laboratory or be accompanied by a research assistant in order to assure your safety after consuming a sleeping aid. Your family is welcome to visit with you in the laboratory after your tests are complete.

In order to monitor your sleep each night, we will connect small sensors to your scalp which will permit us to monitor the electrical activity from your brain. Before the sensors are applied, your scalp will be cleaned with acetone to ensure good sensor placement. The sensors will be attached with collodion and filled with electrode gel to aid in recording of your brain waves. You may feel a slight discomfort when your scalp is cleaned, however, this will be very mild and will dissipate rapidly. If you feel any irritation once the sensors are removed, an emollient with an antibiotic will be applied to the affected area(s). The sensors will be attached on Monday evening and will remain

Participant's Initials _____
Witness's Initials _____

attached until the end of the protocol. This is necessary since reapplication of the sensors each day will result in tender areas on the scalp from the frequent cleaning. Each night you will be administered either the sleeping aid, placebo, or no drug. You will sleep in a private bedroom each night.

We may awaken you during the night to simulate an emergency flight scenario and you will be required to fly the simulator for up to 2 hours. We cannot tell you whether you will be awakened or if you will be awakened at all in order to preserve the surprise factor. If awakened during the night, you will be allowed to return to bed after the flight and sleep for the remainder of the sleep period. At the end of the sleep period, you will be awakened and the test sessions will begin.

On the last day of the study, the principal investigator will answer any questions you have concerning the study. After release by the principal investigator, you are free to return to your home. You should not consume any alcoholic beverages for 10 hours after leaving the laboratory. If you feel any discomfort upon returning home and for 2 days after your visit to the laboratory, call one of the numbers provided to you.

The medication which you will receive is a standard sleep medication routinely prescribed for people who have problems sleeping. As with any medication, there is the slight possibility of side effects. Please note the possible adverse effects (as listed in the Physician's Desk Reference) of the medication listed below.

Halcion: When taken without going to sleep, the known central nervous system (CNS) effects of Halcion are drowsiness, headache, dizziness, nervousness, lightheadedness, and coordination disorder.

Nausea and vomiting have also been known to occur in less than 5% of the patients reporting symptoms.

In less than 1% of patients, euphoria, tachycardia, tiredness, confusional states/memory impairment, cramps/pain, depression, and visual disturbances have been reported.

In less than 0.5% of patients, constipation, taste alterations, diarrhea, dry mouth, dermatitis/allergy, dreaming/nightmares, insomnia, paresthesia, tinnitus, dysesthesia, weakness, congestion, death from hepatic failure have been reported.

Additionally, the following symptoms have been reported by at least one person since Halcion has been in use (1986): anterograde amnesia with appropriate or

Participant's Initials _____
Witness's Initials _____

inappropriate behavior, disorientation, derealization, depersonalization, clouding of consciousness, dystonia, anorexia, fatigue, sedation, slurred speech, jaundice, pruritus, dysarthria, changes in libido, menstrual irregularities, incontinence, and urinary retention. Factors which may contribute to some of these reactions include concomitant intake of alcohol or other drugs, sleep deprivation, or an abnormal premorbid state.

Other events reported include restlessness, irritability, excitation, increased muscle spasticity, sleep disturbances, hallucinations, aggressiveness, falling, somnambulism, inappropriate behavior and other adverse behavioral effects.

Please note the following requirements for your safety:

1. Do not consume any alcoholic beverages at least 24 hours before your scheduled appointments and at least 10 hours after your final release from the laboratory.

2. Do not take any medications at least 48 hours before your scheduled appointment and at least 12 hours after your final release from the laboratory without specific clearance from the principal investigator and the flight surgeon.

The risks associated with this protocol are listed in the contraindications of the medication you will take. The risk associated with EEG recordings is a possibility of slight skin irritation from wearing the sensors on your scalp. This irritation will be treated with standard skin lotion and will dissipate in a day or two.

You may withdraw from the study at any time without prejudice. Should you choose to withdraw before completion of the study, contact the principal investigator to explain what you would like to do. You may be detained in the laboratory after your request to withdraw if you are presently under a drug condition, or until released by a flight surgeon. Additionally, you may be withdrawn from the study by either the principal investigator or the medical monitor due to lack of adequate data collection, equipment malfunction which corrupts the data, adverse reactions to the medication, or development of illness during the study period. If you choose to complete the study, the benefits to you include an assessment of your sleep quality after taking a sleep medication and an assessment of how well you can fly a simulator after administration of a sleep aid. None of the information obtained from this study which identifies you in any way will be released without your expressed consent. All names and other identifying information will be removed from most of the records and replaced with a subject number for future identification. Complete confidentiality cannot be promised since information concerning your health may be required to be reported to appropriate medical or command authorities. Additionally, regulations require names to remain in some of the records for possible inspection by representatives of the U.S. Army and the Food and Drug Administration.

Participant's Initials _____
Witness's Initials _____

Should any questions/problems occur during the period of the study, you may reach Dr. Lynn Caldwell at 255-6857 between 0700 and 1630, and at 1-735-3344 at other hours.

I have received a copy of this consent form.

Participant's Initials _____
Witness's Initials _____

Appendix B

Principal Investigator and Medical Monitor Screening Questionnaires

EFFECTS OF TRIAZOLAM OF SLEEP INERTIA AND PILOT PERFORMANCE

VOLUNTEER SCREENING QUESTIONNAIRE

NAME_____ SSN _____ RANK _____ DOB _____ AGE _____

PI Questions:

1. Do you use tobacco products? YES NO
2. Have you used tobacco products within the past 2 years? YES NO
3. How many caffeinated beverages do you consume per day? _____
4. Are you currently taking any medications? YES NO If yes, what? _____
5. Do you have a current DA 4186? YES NO
6. Do you have any problems sleeping? YES NO If yes, describe: _____
7. What is the average number of hours you sleep per night? _____
8. What is your normal bedtime? _____ Wake up time? _____
9. Have you ever taken any over-the-counter sleep medications? YES NO

If yes, what kind? _____ How frequently? _____

10. Have you ever taken prescription sleeping medications? YES NO

If yes, what kind? _____ When? _____

How frequently? _____Under what circumstances?_____

11. What is your total flight time? _____
12. How many hours of UH-60 time do you have? _____
13. What is your primary aircraft? _____
14. Qualified for study? YES NO

Study disqualifications:

- Current medications of any kind than cannot be discontinued
- No current Form 4186
- Significant sleep problems
- No routine sleep times
- Tobacco use
- Heavy caffeine use (more than 5 cups per day)
- Ages 21 to 35 only
- UH-60 qualified

If no, describe: _____
COMMENTS:

_____ _____
Principal Investigator Date

EFFECTS OF TRIAZOLAM OF SLEEP INERTIA AND PILOT PERFORMANCE

VOLUNTEER SCREENING QUESTIONNAIRE

MEDICAL MONITOR QUESTIONS:

1. Date of last physical examination: _____
2. Are you on flight status with a current up slip? YES NO If no, why not?_____
3. Are you good health currently? YES NO If no, why not? _____
4. Do you have any medical waivers? YES NO If yes, describe: _____
5. Do you have any profiles? YES NO If yes, describe: _____
6. Do you normally take any medication? YES NO If yes, describe: _____
7. Do you have lactose intolerance? YES NO If yes, describe: _____
8. Have you taken any medication within the past 3 days? YES NO If yes, describe: _____
9. Do you have a current DA 4186? YES NO
10. PHYSICIAN: Reviewed medical records? YES NO
11. PHYSICIAN: Performed physical exam? YES NO
12. PHYSICIAN: Qualified for study? YES NO

Study disqualifications:

Current medications of any kind than cannot be discontinued
No current Form 4186
Tobacco use
Heavy caffeine use
Sensitivities to benzodiazepines
Ages 21 to 35 only
Any condition which will jeopardize the subject if he took a benzodiazepine (please be specific)
UH-60 qualified

If no, describe: _____

COMMENTS:

_____ _____

Medical Monitor Date